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GEORGE MORRIS PIERSOL, M.D.

JOHN H. MUSSER, Jr., M.D.
ASSISTANT EDITOR

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THE
AMERICAN JOURNAL
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ORIGINAL ARTICLES

WHAT THERAPY MEANS.

By Oliver T. Osborne, M.A., M.D.,
PROFESSOR OF THERAPEUTICS, MEDICAL DEPARTMENT OF YALE UNIVERSITY, NEW HAVEN, CONNECTICUT.

Therapy is not a sufficiently studied subject. Books on practice are very generally indefinite and rarely explain the details of treatment, unless it be that of an antitoxin or other brilliant specific. Most teachers of clinical medicine, though brilliant in diagnosis and learned in pathology, glide over the therapy of disease. Hospital teaching is of necessity concerned with serious or unusual ailments and terminal conditions of chronic disease. Even the acute illnesses, such as typhoid fever, pneumonia, and the acute infections, which reach the hospital, occur in a class of people who are very different from those seen in private practice, and in the latter the treatment and management must be very different from that carried out in the hospital. Or, if the patient is found among the poorer classes and in a poor home, and he will not go to the hospital for treatment, again the management of the case must of necessity be very different from that learned by the hospital interne.

A large number of the most common illnesses, all of the serious conditions in their incipiency, and during the possible prevention period a large number of psychic, neurotic, hysterical, functional, glandular, blood, muscle, joint, and nerve disturbances must all be treated by the practising physician, but are never seen in the hospital, and not very satisfactorily in the dispensary.

Hence the above facts, and they are facts, necessitate a continuance of didactic teaching in therapeutics and in the specialites, as many conditions in the latter class never reach the hospital or the dispensary. Clinical surgery alone can be taught only in the hospitals and dispensaries, as a broken leg or an appendicitis are the same in the upper hundred as they are in the lower ten, and the surgical procedures are the same.

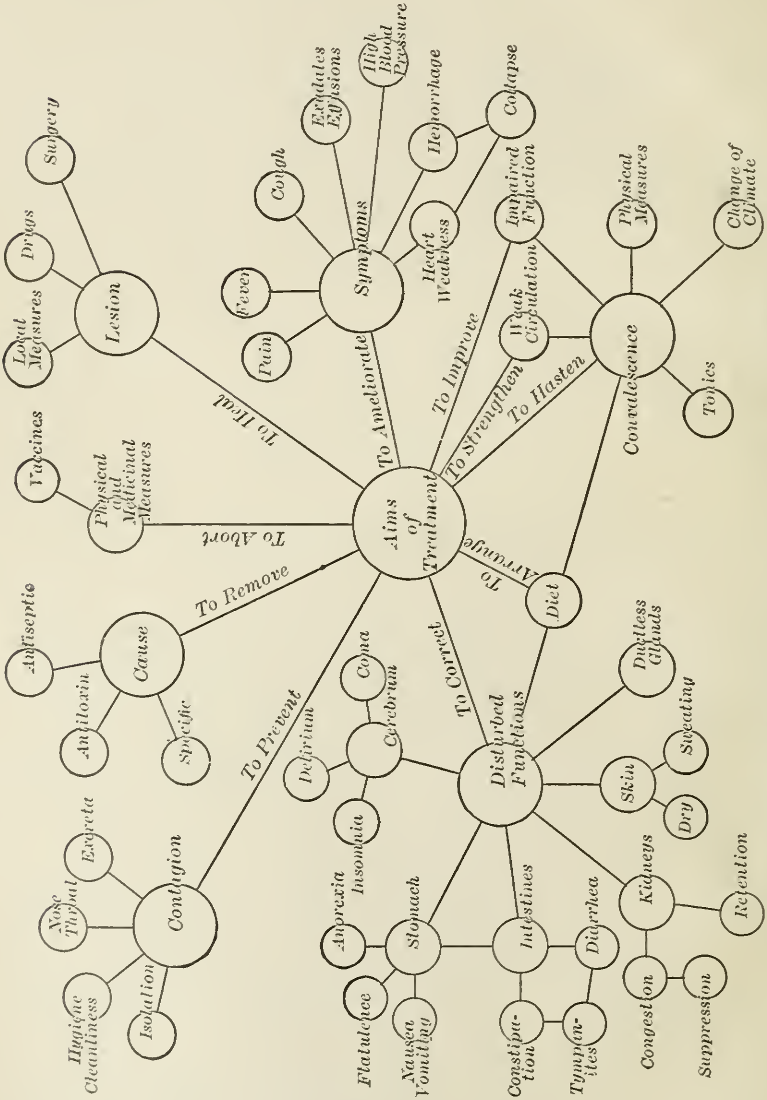

Diagram emphasizing the aims sought in the treatment of any disease or condition.

While there are a number of most excellent books on therapeutics, they are not sufficiently read, and while we have now long ridiculed the old prescription books and the "drug-alone" treatment of disease, we do not sufficiently teach the larger subject of therapy in most of our medical schools, nor does our best medical literature contain enough of good therapy.

To stimulate a more thoughtful consideration of the duties of the physician who is requested to take charge of a patient, and as a basis for instruction in therapeutics to medical students, I have devised the scheme here presented. The object of this diagram is to emphasize the following aims of the treatment of any disease or condition:

1. Not to forget to use every means to prevent the spread of the contagion and the infection of others if the disease is contagious. If the disease is not contagious, the general hygiene and care of the secretions of the nose and mouth and of the excreta are always of more or less importance.

2. If the cause of a disease can be removed or actively combated, that is the part of the treatment that takes precedence of all others.

3. If the disease, or its localization, or its lesion, or a simple condition, as a cold or a headache, can be aborted, that is another primary object of treatment. The direct treatment of the cause (antitoxin, etc.) may do this, or local measures, as ice, heat, hyperemia, leeches, purges, simple surgical measures, etc., or various drugs may so act as to prevent, control, or abort an impending lesion or functional disturbance.

4. A lesion having occurred the patient will not be well until it has disappeared, resolved, or been removed, and hence as soon as a lesion has been established it is the aim of all of our science to eradicate it. Time and nature's own antagonistic and recuperative powers may unaided accomplish this object, but very frequently we can aid and hasten nature's processes by various means. Frequently only surgery can remove a lesion. At other times a lesion becomes permanent and the patient is permanently damaged to that extent. He may be apparently well in spite of this defect or he may be well as long as he so modifies his food, life, and activities; or he may be an invalid; or the lesion may be the cause of his death, sooner or later. However, in any of these eventualities the treatment or management of the lesion and its pathological results is the main object of treatment.

5. Whether or not the lesion can be successfully treated, objectionable or disturbing symptoms must be stopped or ameliorated. No one but the consultant and text-books can refuse to treat symptoms; the practising physician must and should treat the symptoms. The banal phrase of "symptomatic treatment," pointed at with the finger of scorn, must be now recognized as of great

importance under the new name of the "necessary treatment of symptoms." Pain cannot and must not be suffered, lest cardiac depression and exhaustion occur. High, prolonged fever must be reduced, not every little temperature. Too high blood-pressure must be combated, and circulatory failure must be guarded against and combated when present. Almost all acute disease will cease and the patient will recover, provided we can sustain his heart. It is the heart age. The heart fails and the patient dies even before we have got well into our fight against the disease. We have come from the bleeding, vomiting, purging, starving age, through the aconite and alcohol ages, to the feeding and strychnin age. All showing the change of heart both in ourselves and in our patients. Now too much strychnin is given.

6. Students are not sufficiently taught, and the practitioner does not often enough consider the disturbances of function due to, or caused by, the disease that is present. Medical students are so engrossed in the pathology, differential diagnosis, prognosis, and specific treatment, if there is any, as to get the whole idea of the subject under the caption of "the disease," instead of under the caption of "the patient who has the disease." Hence the patient himself and his disturbed physiology or disturbed functions are forgotten, to his detriment. Just what functions may be disturbed, of course, depends on the disease, the lesion, and the prominent symptoms, but it is an axiom that disturbances will occur, and they should be corrected if possible.

The life processes must go on in illness as they do in health, nutrition must be kept up, excretion must occur, repair by sleep must take place, and the organs concerned in these life processes must be coaxed into the greatest efficiency possible with the handicap that they are enduring.

7. The diet must of necessity be modified by the intensity of the illness, the character of the illness, and the condition of the organs of digestion. The food and drink must always be carefully considered, regulated from day to day to meet the conditions, and then gradually increased during convalescence, or perhaps be modified by a lesion that is permanent.

8. Of course, we wish to hasten convalescence, but have we always carefully enough studied our partially healed patients to scientifically decide just what rapidity in the complete recovery we should expect? Generally we have not done so.

A too low systolic blood-pressure, below 105 mm. in an adult, should prohibit his sitting up and certainly his attempting to walk. Too many long, tedious heart weaknesses from strain occur after operations and after severe illnesses because patients are allowed to get up too soon. The appendix patient up and out in ten days is a cardiac and abdominal risk that should not be advocated.

Again, all physical means of massage, graded exercise, fresh air, change of scene and of climate, or location at least, should be considered in hastening recovery and making that recovery complete.

Unfortunately most all charitable hospital and sanatoria patients are sent home too soon. The lack of means makes this a necessity. If some of the charitable and peace funds that are sent abroad were diverted to our own hospitals there would be less suffering, fewer poor, and less excuse for almshouses, orphan asylums, insane institutions, and public charity as a whole.

THE TREATMENT BY SPLENECTOMY OF SPLENOMEGALY WITH ANEMIA ASSOCIATED WITH SYPHILIS.

By H. Z. Giffin, M.D.,
MAYO CLINIC, ROCHESTER, MINNESOTA.

When marked splenomegaly is associated with a history of syphilitic infection or with definitely positive Wassermann tests, a question arises as to the etiological relationship of syphilis to splenomegaly. It is probable that splenic anemia may occur in a patient who has had syphilis in whom it cannot be demonstrated that the syphilis is a definite factor in the condition; on the other hand, it would seem quite proper to separate from other forms of splenomegaly those cases in which syphilitic cirrhosis of the liver exists, gummata of the liver are present, or repeated positive Wassermann tests together with other evidence of infection are obtained.

The grouping of cases should be "away from" splenic anemia in order that every endeavor be made to arrive at as accurate a diagnosis as is possible. Cases classified as splenic anemia should quite definitely conform to that syndrome. By carefully distinguishing the other diseases that are associated with splenomegaly our knowledge will be advanced. Hemolytic jaundice, the portal and biliary cirrhoses of the liver, chronic septic splenomegaly, the splenic anemia of infancy (von Jaksch's disease), endotheliod splenomegaly (Gaucher's disease), lymphoma and lymphosarcoma are the more important entities that have been, and are at the present time, confused with splenic anemia; and in some cases differentiation is impossible even after a study of the pathology. Similarly, cases of splenomegaly in patients with syphilis are to be carefully studied in order that they may be properly classified.

Osler[1] records 3 cases of syphilis with the picture of the Banti type of splenic anemia. Two of these came to autopsy. One a boy, aged eleven years, had been under observation for four years before death. A greatly enlarged spleen and a scarred cirrhotic liver containing several small gummata were found. The patient had had hematemesis, and presented nodes on the shin, a syphilitic arthritis, and ascites. The Wassermann test was negative and a secondary type of anemia with leukopenia was present. The second case was that of a woman, aged twenty-two years. A scarred liver, ascites, and a severe anemia were present. There was no history of acquired syphilis, and the case was seen before the days of the Wassermann test. The third case occurred in a man, aged thirty-four years, who came neither to operation nor autopsy. There was a history of syphilitic infection. A severe anemia was present, the liver seemed to be fissured, and the spleen extended to the level of the iliac spine.

Anderson,[2] Caussade and Levi-Franckel,[3] and Queyrat[4] have reported in all 3 additional cases simulating the Banti type of splenic anemia. These patients were all definitely syphilitic. None of them were operated on, but one came to autopsy.

Diffuse, *non-gummatous hypertrophy* of the spleen quite frequently occurs in patients with syphilis. In adults it is often associated with gummata of the liver or a definite cirrhosis. *Gummata* of the spleen may be miliary or solitary in character. *Gummatous cicatrices* cause a greatly enlarged organ, and *amyloid spleen* has been found in chronic cases. Moxon[5] has reported a case of *acute splenitis* associated with syphilitic pneumonia, a finding which is evidently exceedingly rare.

Enlargement of the spleen in early syphilis is probably quite common. Wile and Elliott,[6] in a review of 100 cases of early syphilis, found 36 with palpable spleens. In none of these cases was enlargement of the liver present. Splenic enlargement in early syphilis usually tends to disappear, but may persist longer than any other visceral manifestation.

Syphilitic splenomegaly during the first eighteen months of life, and especially during the first three months, is common. From two years to twelve years of age, undoubted cases are relatively rare. Up to the age of six months, splenic enlargement appears in 40 per cent. of syphilitic babies. Carpenter,[7] in a review of 348 cases of splenomegaly in infants and children under twleve years of age, found 57 cases of undoubted syphilis with enlargement of the spleen. He concluded that syphilis was second only to rickets as a cause of splenomegaly in infancy.

Hutchinson,[8] in a report of 22 cases of splenic anemia of infancy (von Jaksch's disease), found 4 with congenital syphilis. Weller[9] in a report of 30 cases of the splenic anemia of infancy found 8 to be syphilitic. Syphilis in infants may be associated with blood findings similar to those of the splenic anemia of infancy just as in adults it may be associated with blood findings similar to those of the adult type of splenic anemia. This difference in the blood picture is probably due to a peculiar reaction of the infant's hemopoietic system to disease (Giffin[10]).

Gummatous affection of the spleen is very rare in children and extremely rare in infants. It is usually associated with gummata elsewhere. Still[11] collected 4 cases from the literature and reported 2 cases of his own.

In adults, gummata of the spleen are also of rare occurrence. Still,[11] in 1897, was able to collect only 21 cases from the literature. Martin[12] reported a case in which two or three small gummata were found in the spleen in association with multiple gummata throughout the liver and a marked anemia. It is probable, however, that careful examination of the pathological tissue would show a somewhat greater frequency for gummata of the spleen in adults than now appears on a study of the literature.

It is a striking fact, nevertheless, that in adults as well as in children syphilitic splenomegaly is most frequently of a diffuse, non-gummatous character. It is also well-known that syphilitic splenomegaly may persist or recur in spite of the most active antisyphilitic treatment. Moreover, the severe secondary type of anemia that is frequently present in these cases may not improve with medical treatment. Because of these facts, splenectomy has been performed in three recorded instances and the results would seem to have justified the procedure.

Coupland,[13] in 1886, reported a case of splenectomy for syphilitic spleen. Two years after operation the patient died following hematemesis. Ascites had been present. Autopsy revealed a scarred liver quite typically syphilitic. Hartwell[14] (1913) performed splenectomy on a patient with a severe anemia of the secondary type and a history of hematemesis. The patient denied the possibility of syphilitic infection, but a Wassermann test was strongly positive. Neosalvarsan, mercuric salicylate, potassium iodide, iron, and arsenic had been administered while the patient's condition became less satisfactory. Splenectomy was followed by very prompt improvement. In two weeks the hemoglobin had risen from 25 to 80 per cent. Pathologically the trabeculæ were thickened and large and numerous follicles having fibroid centres were present. Mention of gummata was not made. French and Turner[15] (1914) removed a spleen measuring 7 x 5 inches, and weighing 18 ounces, from a boy, aged five years, in whom there was a blood count suggestive of the splenic anemia of infancy. A Wassermann test had been positive several times and the patient had received antisyphilitic treatment, with no benefit. The patient was apparently well in two months.

In a general review of 58 cases of splenectomy in the Mayo Clinic (July, 1915), 2 cases were briefly discussed in which marked splenomegaly was associated with syphilis (Giffin[16]). One additional patient has been operated on since that time. The histories of these three patients would seem to be of sufficient importance and interest to justify detailed discussion.

Case I (A119102) (Fig. 1).—*Marked splenomegaly; severe anemia; no hematemesis; history of syphilitic infection not obtained; Wassermann, total inhibition; antisyphilitic treatment without definite improvement; splenectomy; treponemata in walls of splenic vessels; excellent health one year later.*

G. H. I., woman, aged forty years; married. First examined November 14, 1914. The family history was negative. She had been married fourteen months and had not been pregnant. She had had catarrhal jaundice at the age of eleven years, typhoid fever at the age of twenty-eight years, and had suffered from many attacks of tonsillitis and quinsy. She stated that her spleen had been enlarged since the typhoid fever twelve years previous; that since that time she had been pale and her complexion had been sallow. As a child, up to the age of fifteen years, she had had an occasional attack of upper abdominal colic without chills, each attack lasting for an hour or two. Four weeks before examination she had suffered from a severe attack of pain in the region of the epigastrium and right costal margin, and was slightly jaundiced after this. There was no history of hemorrhage nor dyspnea, and the patient felt quite strong. There had been a little edema; gastro-intestinal and urinary symptoms were absent. About one year previous to examination a tender swelling had appeared over the anterior

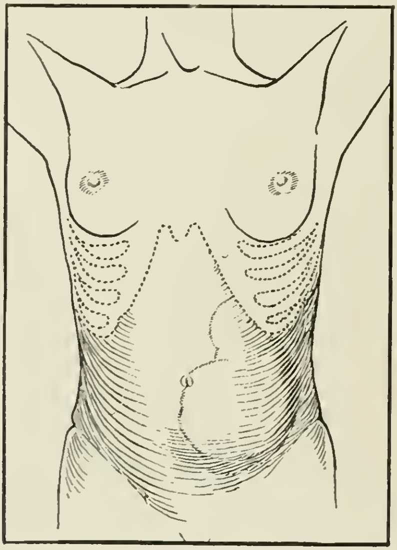

Fig. 1 (A119102).—Position and contour of spleen. Splenomegaly associated with syphilis.

portion of the left chest. This was lanced and later several small pieces of bone were discharged. Six months previous to examination the rib was curetted elsewhere, but drainage had continued up to the time of examination. Antisyphilitic treatment had been administered for six months.

Physical examination disclosed a thin, pale woman; the skin showed a lemon-yellow tint. The weight had been reduced in one year from 130 to 103 pounds. There were small discharging sinuses found in the area of the fifth and sixth left chondrocostal junctures. A large tumor which could easily be recognized as spleen filled almost the entire left half of the abdomen and extended beyond the navel and almost to the symphysis. It was apparently low in position, as its upper pole could be palpated below the left costal margin. The liver seemed to be slightly enlarged on percussion. Examination of the urine was practically negative. The systolic blood-pressure was 106 and the diastolic blood-pressure was 70. Examination of the blood showed a secondary type of anemia, with the hemoglobin at 38 per cent. Red-blood cells numbered 2,950,000 and showed slight anisocytosis. The leukocytes were 6650, and a differential count was not abnormal. Evidence of tuberculosis was not present. A von Pirquet test was negative, and roentgen examination of the chest revealed no pulmonary lesions. A Wassermann test showed total inhibition. On account of the great enlargement of the spleen, and because of the fact that active antisyphilitic treatment had proved unsatisfactory, splenectomy was advised.

Operation, December 4, 1914 (W. J. Mayo). A large spleen measuring 12 x 7 inches and adherent to the diaphragm, stomach, liver and pancreas, was removed through a long left incision. The tail of the pancreas extended up to the hilum of the spleen so that a dissection of about four inches had to be made. The left lobe of the liver was moderately adherent to the abdominal wall, but there was no evidence of cirrhosis. The patient had an uninterrupted convalescence and left the hospital on the eleventh day.

Pathological Report.[17] (L. B. Wilson). Weight of spleen, 900 grams; gland normal in contour, with very marked notch and dorsal groove; external surface slightly nodular; considerable perisplenitis; on section, organ is firm, tough and very dark colored. Microscopically there is a diffuse fibrosis with a moderate lymphocytosis; pulp 3; lymphoid tissue 3; reticulum 3; endothelium of sinuses 2; atrophic pigment 1; amyloid degeneration, 0; arteriosclerosis, 3; adventitia of arteries markedly affected, in some cases amounting to typical gummata; numerous treponemata in vessel walls.

Postoperative Condition. One year after operation the patient's physician stated that she had gained much strength, 15 pounds in weight, and was feeling well. Her blood count was as follows: Hemoglobin, 80 per cent.; erythrocytes, 3,552,000; leukocytes, 11,000. The differential count was not abnormal.

In this case a history of syphilitic infection was not obtained, but a Wassermann test showed total inhibition. The patient was aged forty years, had been married only fourteen months, but had not been pregnant. The spleen was very large and a severe anemia of the secondary type without leukocytosis was present. The liver was not cirrhotic; there had been no hemorrhges. Antisyphilitic treatment had been attended with unsatisfactory results, while splenectomy was followed by prompt improvement and excellent health one year later.

Case II. (A125899 (Fig. 2).—*Moderate splenomegaly; marked anemia of the secondary type without leukocytosis; liver contained palpable gummata; no hematemesis; negative history of lues in both patient and husband; Wassermann test, total inhibition; no improvement of anemia on antisyphilitic treatment; splenectomy; prompt improvement in general health and blood.*

H. S. D., a woman, aged thirty-two years; married; was first examined March 6, 1915. The family history was negative. For the last ten years menstruation had occurred irregularly, from one week to three months apart. Several hemorrhages occurred which her physician had interpreted as miscarriages. She had had scarlet fever at nine years of age, pneumonia at eighteen years; frequent attacks of tonsillitis as a child. Tonsillectomy had been done at the age of fifteen years. The patient complained chiefly of upper abdominal pain and profuse and irregular menstruation. She had been more or less of an invalid for ten years. Her complaints had been quite varied and often of an obscure character. There was a history of chills at frequent intervals. She had taken large quantities of quinin, but plasmodia had never been demonstrated in the blood. There had been frequent attacks of bronchitis, with evening fever and night-sweats, and she had been treated for tuberculosis, although there had never been positive evidence of this disease. For seven or eight years a cramping of the muscles had recurred in various parts of the body at frequent intervals. For the past five or six years soreness and tenderness had been present in the upper abdomen, at times causing considerable complaint and aggravated by pressure. She had never had an acute abdominal colic. The sensitiveness over the upper portion of the abdomen had been more pronounced for six months prior to examination. She had not known that the liver and spleen were enlarged.

Physical Examination. The patient was moderately thin and anemic. Examination of the heart and lungs was negative, and stereoscopic plates of the lungs failed to disclose any evidence of tuberculosis. The liver extended two inches below the right costal margin and hepatic dulness measured about six inches in the right mammillary line. In the epigastrium two irregular masses could be seen to move downward with respiration. These were easily palpable and apparently located in the liver. The spleen was enlarged to the level of the navel and its surface was smooth; splenic dulness measured 9 x 17.5 cm. Abdominal fluid did not seem to be present. There was extreme tenderness to palpation over the entire upper abdomen. Examination of the urine was negative. The systolic blood-pressure was 126 and the diastolic 86. An examination of the blood showed a hemoglobin percentage of 50. The red-blood count was 4,090,000; the leukocyte count 6200; the differential count was not abnormal. A Wassermann test showed total inhibition and was repeated with a positive result.

The patient remained under observation for one month, during which time she received three injections of neosalvarsan, and mercurial inunctions and potassium iodide. She gained somewhat in strength and 7 pounds in weight. The hemoglobin, however, remained low (58 per cent.) and the size of the spleen was not reduced although the liver seemed to be smaller.

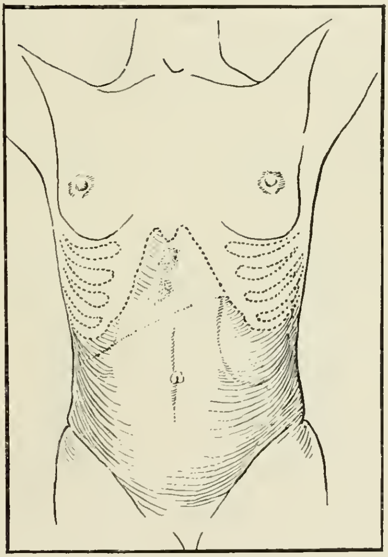

Fig. 2 (A125899).—Position and contour of spleen and liver. Splenomegaly associated with syphilis.

Operation. Splenectomy was decided upon and performed April 1, 1915, by W. J. Mayo. A spleen weighing 670 grams, and measuring 9 x 6 inches and quite adherent was removed through a left lateral incision. There was a small amount of free fluid present in the abdomen. The liver showed extensive cirrhosis. Gummatous tumors were present and the liver was divided into large lobes by irregular contractions. The liver was approximately three-fourths normal size. The tumors were typically gummatous in character, and one the size and shape of a gall-bladder was present in the left lobe.

Pathological Report (L. B. Wilson). Weight of spleen, 670 grams, gland long and slender: no notch; slightly roughened surface; considerable perisplenitis; on gross section organ is pale and firm, but not tough. Microscopically there is a moderate diffuse fibrosis; pulp, 2; lymphoid tissue, 2; reticulum, 3; endothelium of sinuses, 2, swollen; pigment, 0; small amount of amyloid degeneration; arteriosclerosis, 2.

Postoperative Course. Recovery from the immediate operation was uneventful and the patient was discharged from the hospital on the twelfth day. Eight months after operation the patient had improved markedly in weight and strength and the anemia had disappeared.

This patient presented a very irregular and indefinite history. Positive evidence of luetic infection could not be obtained, but the Wassermann tests were strongly positive. The spleen was moderately enlarged and non-gummatous. The liver contained palpable gummata. The anemia was marked and of a secondary type without leukocytosis. There was no history of hemorrhages. Active antisyphilitic treatment for one month caused no improvement of the anemia while splenectomy was followed by very definite improvement.

CASE III (A140128) (Fig. 3).—*History of syphilitic infection at twenty-one. Three positive Wassermann tests elsewhere during the last two years; Wassermann test negative at the time of examination; moderate splenomegaly; slight anemia; recurrent hematemesis; long continued antisyphilitic treatment attended with only partial relief; splenectomy. One gumma and a few treponemata in spleen; excellent condition three months later.*

H. P., male, aged thirty-five years; single. Examined September 2, 1915. Family history negative. The patient had had a preputial sore at the age of twenty-one and three attacks of gonorrhea. There was a negative history for other severe diseases. Six years previous he had been jaundiced for two months and thinks the skin had never entirely cleared after that time. He had gradually lost weight from 210 pounds to 170 pounds and had not had his former good general health. Two years previous to examination an ulcer had formed on the right shin. A large spleen and a very large liver were discovered two years before examination. The hemoglobin was 60 per cent. At that time he was complaining of left-side headache, usually worse from 4 to 10 P.M.; pain in the left arm and left leg. Several nodules formed in the left frontal region. From one to three times a week he had severe chills. One and a half years previous the pain in the head, arm and leg were so severe that morphin was necessary. At this time there was an effusion into the right knee-joint. Salvarsan was given; about two days later a severe attack of hematemesis resulting in unconsciousness occurred; after recovery from this his pain had disappeared. Since that time salvarsan intravenously and mercury intramuscularly had been administered. His general health was then quite good until eight months before examination, when a second severe gastric hemorrhage occurred. This had been followed every two or three weeks by nausea and black stools.

Physical Examination. The patient was well nourished and weighed 173 pounds. The left frontal region of the skull was irregularly depressed. The spleen filled the entire left upper quadrant of the abdomen and was smooth; liver dulness was apparently not increased. A notch of the spleen was palpable while the edge was indefinite. Scars were present on the right shin. Examination of the urine was negative. The systolic blood-pressure was 118 and the diastolic 72. Examination of the blood showed a hemoglobin of 85 per cent.; red-blood count of 4,240,000; leukocytes, 4900; differential count was not abnormal; coagulation time was five minutes. Test meal showed slight hyperacidity. Fluoroscopic examination of the stomach presented evidence suggestive of duodenal ulcer (duodenum was negative at operation) Wassermann test was negative. Three positive Wassermann tests had been obtained elsewhere during the last two years.

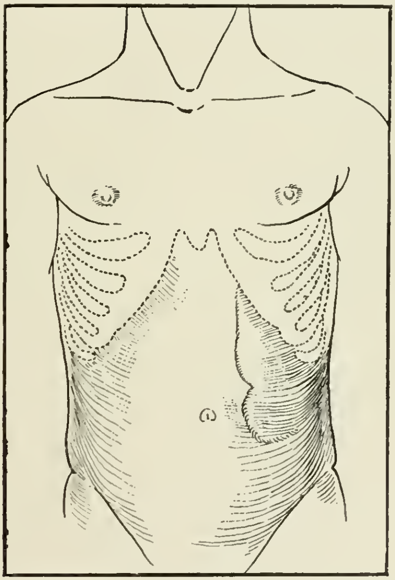

Fig. 3 (A140128).—Position and contour of spleen. Splenomegaly associated with syphilis.

The physician who referred this patient stated that while his Wassermann test had become negative and he had improved to a considerable extent under salvarsan and mercury, on the other hand improvement reached only a certain point and then his recovery seemed to be at a stand-still. (I am indebted to H. B. Anderson, of Toronto, for complete notes upon this case.)

Operation. Splenectomy was decided upon and performed September 13, 1915, by D. C. Balfour. A spleen five times normal size was removed through a left lateral incision. The liver was small and deeply fissured so that portions of the organ appeared almost like separate masses. There was marked obstruction of the portal circulation as evidenced by the varicosities in the round ligament. Stomach, duodenum and gall-bladder were negative.

Pathological Report (L. B. Wilson). Weight of spleen, 1050 grams; notch distinct, capsule slightly thickened; on section, firm, tough, hard, showing general fibrosis. Microscopically there is an intense diffuse fibrosis, 3; pulp, 2; lymphoid tissue, 1; reticulum, 4; endothelium of sinuses, 2; pigment, 1; amyloid degeneration, 2; arteriosclerosis, 3; affecting principally adventitia; 1 typical gumma near vessel, involving wall; a few treponemata.

Postoperative Condition.—The postoperative course was uneventful save for the appearance of a rather severe capillary bronchitis beginning on the sixth day. As a result of the coughing a resuturing of the abdominal wound was necessary two weeks after operation. The patient was discharged in satisfactory condition four weeks later. A Wassermann test done six weeks after operation was negative. Three months later the patient was in excellent condition with hemoglobin at 90 per cent.

This patient presented a history of syphilitic infection and during the course of his illness had had three positive Wassermann tests. There had been two attacks of severe hematemesis. Marked splenomegaly, and an advanced cirrhosis of the liver, apparently syphilitic, were present. The anemia had been recurrent. Very prompt improvement followed splenectomy.

The three cases of splenomegaly herewith reported are definitely associated with lues. Cases undoubtedly occur, however, in which a luetic history is obtained which seems to have no etiological relationship to the splenomegaly. As an instance of this occurrence, the following brief abstract may be given:

(A89075).—*N. B. S., man, aged thirty-five years, married. Examined August 3, 1913; definite history of syphilis with secondaries ten years previous; onset of present illness sudden with severe hematemesis six weeks previous to examination; recurrence of hematemesis ten days before examination; a third hemorrhage nine days before examination; hemoglobin, 35 per cent.; secondary type of anemia; red-blood cells, 2,410,000; leukocytes, 4900. Marked enlargement of the spleen; ascites; gradual improvement followed by splenectomy.* A spleen measuring 10 x 9 inches and weighing 1030 grams was removed. Microscopically there was a diffuse hypertrophic fibrosis. The liver was of normal size and showed no evidence of syphilitic cirrhosis.

This patient presented a definite history of syphilis followed by active treatment and apparent cure. Ten years later sudden severe hematemesis occurred. Marked splenomegaly with ascites was found. A severe secondary type of anemia and negative Wassermann tests completed the typical clinical picture of splenic anemia of the Banti type. At the time of operation no evidence of syphilitic cirrhosis was found.

SUMMARY. 1. It is probable that the syndrome of splenic anemia and Banti's disease may be present in a patient who has had syphilis, in whom it cannot be demonstrated that the syphilis is a definite etiological factor in the condition.

2. Cases of marked splenomegaly in which syphilitic cirrhosis of the liver, or gummata of the liver, are present, or in which repeated positive Wassermann tests together with other evidence of infection are obtained, should be separately classified and studied.

3. Because of the fact that syphilitic splenomegaly with secondary anemia has persisted in spite of active antisyphilitic treatment, splenectomy has been done elsewhere in 3 recorded cases. Three additional cases of this character are herewith reported.

4. The results following splenectomy for marked splenomegaly associated with syphilis and anemia performed after a trial of antisyphilitic treatment seem to have justified the procedure in these few instances.

5. The 3 cases herewith recorded showed prompt improvement after splenectomy and were in excellent condition three months, eight months, and one year respectively from the date of operation.

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ON THE COMPARATIVE TOXICITY OF MORPHIN AND MORPHIN-NARCOTIN (NARCOPHIN).[1]

By David I. Macht, M.D.,
BALTIMORE, MARYLAND.
(From the Departments of Pharmacology and Medicine, Johns Hopkins University, Baltimore.)

The difference in the pharmacological action of the alkaloid morphin or its salts and the galenical preparations of opium has in the last few years been attracting considerable interest. The explanation of this difference in action, and, in general, the relative pharmacodynamic values of the opium alkaloids individually and in combination with each other, sometimes spoken of as the "opium problem," has been the subject of investigation on the part of various pharmacologists, notably of Sahli,[2] Faust,[3] Bürgi,[4] and Straub.[5] Among the most interesting and important contributions on the subject are those of the last-named observer. Straub and his pupils Hermann[6] and Caesar,[7] called attention to the interesting synergism exhibited by the two principal alkaloids of opium in point of quantity, namely, morphin and narcotin. Narcotin Straub regards as a particularly inert body, yet, when that inactive substance is combined with morphin, he found the properties of the morphin to be many times intensified, or, as he expresses it, "potentiated." Thus, for instance, Straub found that the lethal dose of the morphin-narcotin combination for a white mouse is 0.0025 gm., a quantity much less than that of morphin alone, which is 0.015 gm.

Again, the combination of morphin and narcotin was found to affect the respiration much more efficiently than morphin alone. This synergism of morphin and narcotin Straub regards as responsible for the difference in action between morphin and opium.

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[1] This investigation has been endowed by a grant from the Council on Pharmacy and Chemistry of the American Medical Association.

[2] Therap. Monatsh., 1909, No. 1.

[3] München. med. Wchnschr., 1910, Nos. 1 and 2.

[4] Deutsch. med. Wchnschr., 1910, Nos. 1 and 2.

[5] Biochem. Ztschr., 1912, xli, 419. [6] Ibid., xxxix, 216. [7] Ibid., xlii, 316.

His work was criticized by Meissner.[8] Nevertheless, a combination of morphin and narcotin meconates under the name of narcophin was put on the market and is being used by various clinicians. A careful analysis of the pharmacological action of the principal opium alkaloids individually and in combination with each other on various physiological functions, circulation, respiration, etc., has been carried on by the author of the present paper for some time, and some of the results have already been published,[9] and still others are to appear later. In the present investigation the author has attempted, at the suggestion of the council on Pharmacy and Chemistry of the American Medical Association, to determine the relative toxicity of large quantities and the lethal dosage of morphin and morphin-narcotin or narcophin. This was deemed especially desirable, as the lethal dosage of the latter drug has been determined by Straub for white mice only.

ANIMALS STUDIED. Inasmuch as it is a well-known pharmacological fact that the action of narcotic drugs on various animals shows considerable variation among various species as compared with each other, an effort was made to test the action of the two drugs on a large variety of animals in order that the results might be of greater value for therapeutic application. Accordingly, in the present research the action of morphin and narcophin was observed in the following animals: frogs, fishes, turtles, white mice, white rats, guinea-pigs, rabbits, birds, cats, and dogs.

Purity of the Drugs. The alkaloids used were the purest obtainable on the market, and the percentage of impurities in them was too small to vitiate the results.[10]

Action on Frogs. The effect of narcophin on frogs can perhaps be best understood by bearing in mind the individual actions of the constituent alkaloids morphin and narcotin.

The effect of morphin has been well described by earlier writers and is well known to every student of pharmacology. The action is divided into two stages, the narcotic and the tetanic. On administering a large dose of morphin there is, first, a diminution of spontaneous movement, which is followed by incoördination and more or less narcosis. Following this narcotic stage, in an hour or two, the reflexes become active again and the animal soon develops convulsions, from which it may gradually recover or become exhausted and die.

The effect of narcotin has been clearly described by von Schröder.[11] On injection of this alkaloid we note also two stages, a narcotic and a convulsive one. The narcosis, however, is not

[8] Biochem. Ztschr., 1913, liv, 395.

[9] Macht, Jour. Am. Med. Assn., 1915, lxiv, 1489; Jour. Pharmacol. and Exp. Therap., 1915, vii, 338; and 1916, viii, 1.

[10] See L. E. Warren, Amer. Jour. of Pharmacy, 1915, lxxxvii, 439.

[11] Arch. f. exp. Path. u. Pharmakol., 1883, xvii, 96.

deep and is of very short duration, whereas the tetanic stage is very marked and leads to paralysis and death.

The effect of a combination of morphin and narcotin salts, such as the meconates (narcophin) or others, may be regarded as a summation of the individual morphin and narcotin effects.

On injecting a fatal dose of narcophin (about 1 mg. per gram.) into the lymph sac of a frog we also note a narcotic and a tetanic stage. The narcotic stage sets in more quickly than after morphin alone, and the narcosis is much more marked. It generally, however, lasts a shorter time than the narcotic stage following morphin. The second or tetanic stage soon supervenes, which is of a more violent character than that produced by morphin. The animal is soon exhausted and dies from paralysis of the spinal cord.

The following protocols will illustrate the toxic action of narcophin as compared with morphin. (Experiments 1 and 2.) It will be seen from experiment 2 that 25 mgs. of narcophin (consisting of about 8 mgs. of morphin meconate plus 17 mgs. of narcotin meconate) is much more toxic than 25 mgs. of morphin sulphate administered alone. The combination of morphin and narcotin (narcophin) corresponds in toxicity, therefore, to the same weight of morphin, and is much more toxic than the amount of morphin meconate it contains would be alone. Inasmuch as the average fatal dose of narcotin is about 2 mgs. per gram weight of frogs, the toxicity of narcophin for frogs is equivalent to the arithmetical sum of the toxicity of its two components:

Experiment 1. July 8. Frog, 25 gms.

1.35 P.M.	Injected morphin sulph. 25 mgs. in 1 c.c. saline in dorsal lymph sac.
1.40	Slight sluggishness of reflexes.
1.42	Deeper narcosis.
2.00	Deep narcosis.
2.24	Reflexes getting more excitable.
2.40	Convulsions.
2.50	Tetanus followed by paralysis.
2.55	Dead.

Experiment 2. July 8. Frog, 24 gm.

1.36 P.M.	Injected narcophin 25 mgs. in 1 c.c. saline in dorsal lymph sac.
1.40	Deep narcosis; no response to touch.
1.45	Hyperexcitable; spasmodic movements on rapping on the table.
1.47	Spontaneous tetanic convulsions.
2.08	Paralyzed.
2.12	Nervous system dead; no response to stimulation.

An interesting observation made in connection with the effect of narcophin on the frog is its action on the heart as compared with that of morphin.

It was noted that morphin is more toxic to the frog's heart when given alone than when combined with narcotin. Thus, after morphin injection the heart was seen to beat feebly and, curiously enough, there was a difference in the rhythm of the beats between the sinus and the ventricle. Heart blocks of 2 to 1, 3 to 1 and 4 to 1 were observed. Narcophin, on the other hand, had no such effect. It caused a slowing of the heart beat, but no heart block, and the heart continued to beat for a longer time than after morphin. The following two protocols will illustrate these phenomena. (Experiments 3 and 4.)

Experiment 3. Frog, 27 gms.

11.45 A.M. Injected morphin sulphate 50 mgs. in 2 c.c. saline in abdominal lymph sac.
11.50 Very little change.
11.53 Distinct narcosis; does not respond well to stimulations of touch, etc.
11.55 No response to rapping on table.
12.05 P.M. Same.
12.10 Still, narcotized deeply.
12.15 Placed on back, cannot turn over; reacts but slightly to touch.
12.18 Spontaneous clonic convulsions.
12.23 Same, chest opened; heart shows ventricle beating feebly.
12.30 Paralyzed. Heart shows sinus beating 40 per minute, ventricle, 10 per minute.
12.34 Venous sinus and auricle contract 36 per minute; ventricle, 9 per minute.
12.48 Reflexes all gone; heart still going.
1.05 Dead.

Experiment 4. Frog, 28 gms.

11.44 A.M. Injected narcophin 50 mgs. in 2 c.c. saline in abdominal lymph sac.
11.50 Narcosis beginning.
11.53 Deep narcosis.
11.56 Beginning hyperexcitability; spasmodic movements and jumping on lightly rapping the table.
12.05 P.M. Beginning paralysis; very toxic.
12.10 Same.
12.15 Paralyzed; no response to stimulation.
12.25 Chest opened. Heart beating well, 16 per minute; no heart block.
12.30 Heart beating forcibly 20 per minute; no heart block.
12.34 Heart beating forcibly 32 per minute; no heart block.
12.48 Heart still beating well.
1.15 Heart still beating well.

Action on Fishes. Fish have not been employed as much in pharmacological experiments as they perhaps should be. They are especially interesting in studying the action of opium alkaloids, as the effect on respiration can be conveniently observed by watching the movements of the gills. Charvet[12] made use of gold fish in an early work on opium alkaloids, and Dreser[13] used them in his work on heroin. Russian pharmacologists often employ large fishes for studying the action of drugs on the circulation of the gills. The comparative action of morphin and narcophin was studied by me on small gold fish, and is illustrated by the accompanying protocols. (Experiments 5 and 6.)

The fish were placed in solutions of the drugs in fresh tap water. It will be seen that narcophin is much more toxic for fish than is morphin. That the synergism of morphin and narcotin is responsible for the increased toxicity of narcophin is evident from Experiment 7, showing the action of narcotin alone. A combination of other salts of morphin and narcotin was found to have exactly the same effect as narcophin.

Experiment 5. June 29, 1915. *Carasseus aureus.*

11.50 A.M. Placed in 0.1 per cent. solution of morphin sulphate.
11.55 Swimming around lively. Respirations 125 per minute.
12.00 M. Movements a little sluggish. Resp. about 100 per minute.
12.10 P.M. Same.
12.13 Same. Respirations 84 per minute.
12.20 Same.
12.30 No change.
1.05 Remains stationary, breathing slowly; taken out and placed in fresh water.
Next day Complete recovery.

Experiment 6. *Carasseus aureus.*

11.50 A.M. Placed in 0.1 per cent. of narcophin.
11.55 Swims about lively. Respirations, 120.
11.58 Quiet; respirations, 48 per minute.
12.00 Lying on side, poisoned.
12.20 Dead.

Experiment 7. *Carasseus aureus.*

3.55 P.M. Placed in solution of narcotin hydrochloride 0.1 per cent.
3.57 No change.
4.00 Lying on side, obviously toxic, breathing very rapid.
4.06 Breathing more slowly; lies still, but from time to time makes sudden convulsive movements.
4.15 Dead.

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[12] Die Wirkung des Opiums und seine constituirenden Bestandtheile, 1827.

[13] Pflüger's Archiv, 1898, lxxii, 485.

Experiments on Terrapins. The comparative toxicity of morphin and narcophin for these animals was somewhat different from that observed in fishes. In my experiments I used small terrapins 4 to 5 cms. long. These were placed, like the fish, in dishes with shallow layers of the drug solution. It was found that the terrapins when placed in a solution of 0.1 per cent. morphin sulphate died in two hours. To produce death in the same period of time it was necessary to employ a 0.2 per cent. of narcophin, or morphin-narcotin meconate. Inasmuch as narcophin contains about 33 per cent. of its weight of morphin, it will be seen that narcophin is a little more toxic for terrapins than the amount of morphin it contains would be alone.

Experiments on White Mice. The observations on mice, which were the smallest mammals studied in the present work, were interesting from two points of view, both of which have already been described by Straub and his pupils. In the first place, Straub called attention to a remarkable specific biological reaction to morphin noted in mice. He found that after small doses of morphin the animal's tail passed into a curious stiff condition described by him as a state of katatonia. The tail is bent backward or curled spirally, and remains remarkably stiff in that position for a long time. The minimal dose of morphin inducing such a stiffening of the tail is given by him as 0.01 mg., but he remarks that the dosage varies in different strains of mice. Narcophin was found by Straub to give this reaction in much smaller (0.0025 mg.) doses, whereas narcotin does not give the reaction at all.

The smallest dose of morphin which I found to give the reaction in one strain of mice was 0.01 mg. In the same strain of mice 0.02 mg. of narcophin (=0.006 mg. morphin meconate +0.012 mg. narcotin meconate) gave a distinctly positive result.

In another strain of mice I found 0.1 mg. of morphin and 0.2 mg. narcophin required to give the minimum positive reaction.

In the second place, Straub found that the fatal dose of narcophin for mice was much less than that of morphin. This observation I was able to corroborate in my experiments. It required an average from 10 to 20 mgs. of morphin sulphate to kill a mouse of about 30 gms. weight in from one-half to two hours. It took exactly the same weight of narcophin, in other words, about one-third as much morphin in combination with narcotin, to produce death in the same time. It required from 35 to 50 mgs. of narcotin hydrochloride alone to produce death in about six hours. It is, therefore, apparent that the toxicity of morphin for mice is distinctly *potentiated* by narcotin, just as described by Straub.

Experiments on Rats. White rats were used. The results were somewhat different from those obtained in mice. It was found that 2 mgs. of morphin sulphate per gram weight of rat produced death in about one hour. The same dosage of narcophin proved also fatal, though after a much longer period of time (over six hours). The toxicity of narcophin for rats, weight for weight, is therefore less than that of morphin. The explanation of this difference is to be found probably in its less depressant action on the respiration. The following two protocols will illustrate strikingly this difference:

Experiment 8. July 8. White rat, 185 gms.

10.50 A.M. Injected intraperitoneally, 75 mgs. morphin sulphate in about 3 c.c. saline solution. Respirations, 140 per minute.
11.05 Deep narcosis; tail stiff. Respirations, 36 per minute.
11.15 Same. Respirations, 32 per minute.
11.25 Eyes bulging, very slow breathing, Respirations, 28 per minute.
11.30 Same. Respirations, 20 per minute.
11.34 Dead.

Experiment 9. July 8. White rat, 109 gms.

11.05 A.M. Injected intraperitoneally 50 mgs. narcophin in about 2 c.c. saline solution. Respirations, 140 per minute.
11.15 Standing quiet. Respirations, 96 per minute.
11.25 Same. Respirations, 84 per minute.
11.30 Narcotized distinctly. Respirations, 64 per minute.
11.35 Respirations improve. Respirations, 80 per minute.
11.40 Respirations improve. Respirations, 88 per minute.
11.50 Breathing about 88 respirations per minute.
12.10 Tail stiff. Respirations, 76 per minute.
12.55 Lies quietly. Respirations, 80 per minute.
1.25 Same. Respirations, 84 per minute.
1.50 Same. Respirations, 72 per minute.
4.50 In good condition. Respirations, 80 per minute.

Next day, found dead.

Experiments on Guinea-pigs. These animals, like rats, were also found to be very resistant to the effects of the opium alkaloids. The injections were given subcutaneously at intervals of from ten to twenty minutes, administering 25 to 50 mgs. of the drug at a time. It was found that the lethal dose of morphin sulphate was on the average about 1.5 mgs. per gram weight of guinea-pig and that of narcophin very much the same, or 1.6 mgs. per gram weight. Six hundred milligrams of narcotin hydrochloride alone administered to a guinea-pig weighing 550 gms. resulted in death on the following day. This made the average lethal dose of narcotin about 1.1 mgs. per gram weight. It will be thus seen that the lethal dose of narcophin is considerably greater than the arithmetical sum of the toxic doses of its two constituents, morphin and narcotin. This lesser toxic effect is probably also to be attributed to its less depressant influence on the respiration. It was found that morphin reduced the respiratory rate from 120 to 48 per minute, whereas the greatest reduction after narcophin was found from 120 to 88 per minute. Narcotin alone not only did not slow the respiratory movements, but actually deepened and accelerated them. The less depressant action of narcophin thus seems to be due to the synergistic action of its two constituents.

Experiments on Rabbits. The comparative toxicity of morphin and narcophin for rabbits is of especial interest, as many of our posological data for opium alkaloids are derived from experiments on these animals.

The drugs in our experiments were administered in two ways, subcutaneously and intravenously. It was noted that morphin is much more toxic for rabbits when given through a vein, and thus suddenly thrown into the blood stream in large quantities, than when it was absorbed slowly after subcutaneous injections. The average fatal dose of morphin given intravenously was 0.31 mg. per gram weight of rabbit; and when injected under the skin or intraperitoneally also about the same or 0.32 mg..per gram weight, death occurring in the first case in from thirty to sixty minutes, while in the latter only after three or four hours. The fatal dose of narcophin, however, when injected into a vein was found to be about 0.17 mg. per gram weight of rabbit; whereas administered subcutaneously it was 0.79 mg. per gram weight. It was noted that after intravenous injections of narcophin the animals quickly developed very violent convulsions, from which they died. In one case I have seen a 1000 gm. rabbit succumb to 40 mgs. in less than five minutes. These convulsions were also seen after intravenous morphin injections, but were not so violent and did not come on so quickly. After subcutaneous injections, convulsions were not the striking feature after either drug, except toward the end. On the other hand a remarkable difference in the respiratory function could be noted. The breathing after administration of morphin was powerfully depressed, the respirations becoming shallow and very slow, their number in extreme cases decreasing to one-sixth or one-eighth of the original. After narcophin, on the other hand, the breathing was not so much depressed, the number of respirations never falling to less than one-fourth of the original and the individual respirations were often deeper than normally. (Protocols Experiments 10 and 11.)

Experiment 10. July 15, 1915. Rabbit, 1600 gms.

3.35 P.M. Respirations, 200 per minute. Injected 100 mgs. morphin sulphate in ear vein.
3.40 Respirations, 36 per minute.
3.45 Slight convulsions.
3.55 Respirations, 44 per minute. Injected 50 mgs. morphin sulphate.
4.05 Injected 50 mgs. morphin sulphate.
4.15 Injected 50 mgs. morphin sulphate.

4.25 Injected 50 mgs. morphin sulphate.
4.35 Injected 50 mgs. morphin sulphate.
4.40 Injected 50 mgs. morphin sulphate.
4.45 Injected 50 mgs. morphin sulphate; convulsions.
4.55 Injected 50 mgs. morphin sulphate; violent convulsions.
5.00 Death.

Experiment 11. July 15, 1915. Rabbit, 1350 gms.

2.35 P.M. Injected in ear vein 100 mgs. narcophin. Respirations, 200 per minute.
2.45 Deep narcosis; slight convulsions; respirations, 96 per minute.
3.10 Injected 50 mgs. narcophin; respirations, 75 per minute.
3.25 Injected 50 mgs. narcophin; violent convulsions.
3.26 Dead.

Experiments on Dogs. The drugs were administered to these animals also in two ways, viz., intravenously and subcutaneously, and, as was to be expected, the intravenous toxic doses were much smaller than those required for hypodermic injections. The average fatal dose of morphin in saline solution injected slowly into a vein of a dog under ether was 37 mgs. per kilo, death supervening in about two hours. The fatal dose of narcophin administered in the same way was 173 mgs. per kilo. The fatal dose of morphin by subcutaneous injection was 200 mgs. per kilo while that of narcophin was about 310 mgs. per kilo weight of dog. As compared with narcophin, morphin depressed the breathing to a much greater extent, the number of respirations decreasing to one-fourth or one-fifth of the original. Narcophin produced much less respiratory depression, the number of respirations decreasing about one-half; but, on the other hand, this drug produced earlier and more violent convulsions.

Experiments on Cats. Experiments on these animals are interesting more from a pharmacological than a therapeutic point of view, as it is well known that morphin exerts a peculiar action on cats. When that alkaloid is injected into a cat no narcotic action is produced; on the contrary, the drug acts as a delirifacient and convulsant. One interesting observation in this connection is that noted by Straub. That observer claims that a combination of morphin with narcotin acts upon cats as a narcotic; in other words, if narcophin is injected into a cat, or if narcotin is first injected and is later followed by a dose of morphin, no delirium or convulsions are produced, but the animal is narcotized.

I have endeavored to repeat Straub's experiments, but have only on rare occasions observed such a narcotic action. In most cases a combination of morphin and narcotin acted just like morphin alone; that is, as an excitant, the effects being only somewhat delayed. After small doses (10 to 20 mgs. per kilo) the delirium was perhaps less marked. After large doses of narcophin, however (40 to 50 mgs. per kilo), violent delirium was produced.

In this respect my observations were in agreement with those of Meissner.

Narcophin was furthermore found to be more toxic for cats than the amount of morphin it contains. It was found that 100 mgs. per kilo weight of cat excited the most violent delirium and resulted in death in an hour, whereas a dose of 50 mgs. of morphin per kilo weight of cat also produced violent delirium, but was followed by recovery on the following day. Narcotin alone, injected in quantities of 100 mgs. had no visible effect on the animals. (Experiments 12, 13, 14 and 15.)

Experiment 12. January 25, 1915. Cat, 2.5 kilos.
1.15 P.M. Injected subcutaneously 30 mgs. morphin sulphate.
1.30 Hyperexcitable.
2.00 Violent delirium; frothing at mouth
Delirium lasts all day.

Experiment 13. January 25, 1915. Cat, 2.5 kilos.
1.00 P.M. Injected narcotin hydrochloride, 60 mgs., subcutaneously.
1.30 No effect; sits quietly.
2.00 Injected 30 mgs. of morphin sulphate.
3.00 Lies quietly.
4.00 Violent delirium and convulsions.

Experiment 14. June 28, 1915. Cat, 2.5 kilos.
1.45 P.M. Injected 100 mgs. morphin sulphate subcutaneously.
2.00 Hyperexcitability.
2.15 Delirium.
2.45 Very wild delirium.
3.00 Delirium continues; mouth frothing.
4.30 Same.
Next day
11.15 A.M. Still hyperexcitable.
2.00 P.M. Getting more quiet.

Experiment 15. June 28. Cat, 2.2 kilos.
11.15 A.M. Injected 200 mgs. narcophin.
11.30 Delirium.
12.00 M. Delirium more violent; foaming at mouth; rolls on back in convulsions.
1.15 P.M. Exhausted from convulsions.
2.45 Dead.

Action on Birds. S. Weir Mitchell,[14] in 1869, called attention to an incidental observation in which he noted the extreme resistance of pigeons to morphin. In connection with the present investigation it was interesting to inquire whether a combination of morphin with narcotin acted in the same way. Accordingly, two pigeons were selected and one received injections of morphin sulphate under a wing, while the other was injected with narcophin. It required 250 mgs. of morphin sulphate to produce death which supervened, preceded by convulsions, in about an hour and a half. Narcophin was seen to produce much more toxic symptoms. The animal made convulsive movements after an injection of 50 mgs. It was paralyzed after 200 mgs., and died in convulsions after 250 mgs. of the drug one hour and thirty-five minutes after the beginning of the experiment.

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[14] Am. Jour. Med. Sc., 1869, lvii, 37.

DISCUSSION. The results of the present investigation may, for convenience of comparison, giving the average minimal lethal dose for each animal, be placed together as in the accompanying table.

TABLE OF COMPARATIVE DOSAGE FOR VARIOUS ANIMALS.

Animals.	Minimal lethal. Dose of morphin.	No. of exps.	Minimal lethal. Dose of narcophin.	No. of exps.
Frog	1 mg. per gm. wt.	12	1 mg. per gm. wt.	18
Fish	0.2 per cent. solution	12	0.1 per cent. solution	12
Terrapin	0.1 per cent. solution	3	0.2 per cent. solution	3
White mouse	0.5 mg. per gm. wt.	12	0.5 mg. per gm. wt.	12
White rat	2 mgs. per gm. wt.	3	2 mgs. per gm. wt.	3
Guinea-pig	1.5 mgs. per gm. wt.	3	1.6 mgs. per gm. wt.	3
Rabbit (intravenous)	0.31 mg. per gm. wt.	3	0.17 mg. per gm. wt.	6
Rabbit (subcutaneous)	0.32 mg. per gm. wt.	3	0.79 mg. per gm. wt.	4
Cat	Over 100 mgs. per kilo wt.	6	50 mgs. per kilo wt.	12
Dog (intravenous)	87 mgs. per kilo wt.	4	173 mgs. per kilo wt.	6
Dog (subcutaneous	200 mgs. per kilo wt.	4	310 mgs. per kilo wt.	6
Pigeon	1 mg. per gm. wt.	1	1 mg. per gm. wt.	1

It is well to note that the figures here given are not so much of value as absolute standard toxic or lethal units as giving the relative toxilogical values of morphin and narcophin. The absolute lethal dosage may vary, as is well known, with the strain or breed of the animal used, time of year, etc.; the ratio of toxicity of two drugs, however, performed on two animals of the same lot at the same time remains pretty constant.

It will be seen that the lethal doses for various animals differ enormously, but that in general the fatal dose of narcophin is about the same weight for weight as that of morphin.

Inasmuch as narcophin consists of about 33 per cent. by weight of morphin meconate and 67 per cent. of narcotin meconate, it is obvious that the toxicity of narcophin as compared with the toxicity of the morphin meconate which it contains if given alone is much greater. This greater toxicity can be in some cases, as that of the frog, explained by the arithmetical sum of the effects of its two components. In other cases, however, the morphin and narcotin seem to potentiate each other, in the sense of Straub.

These observations are of importance from a clinical point of view. Of the clinical observers who have so far published their experiences with narcophin (Klaus,[15] Cassel,[16] Hirsch,[17] Kleinberger,[18] von Stalewski,[19] Jaschke,[20] Schlimpert,[21] Zehbe,[22]), some employed it in the same doses as morphin. Others, however, as, for instance, Hirsch, enthusiastically advocate larger doses, 45 to 60 mgs., as innocuous.

In regard to such dosage we would urge caution. Although within toxic limits narcophin may be perfectly harmless even in larger doses than have been so far employed, still it is well to bear in mind that in comparing the therapeutic values of drugs we should be guided by the ratio of the *dosis lethalis*, or lethal dose, to the *dosis efficax*, or dose sufficient to produce a therapeutic effect. What this ratio is for narcophin in the case of man is still an open question.

It is further apparent that the synergism of morphin and narcotin is highly complicated; the same function responding differently to the combination in different animals. Experiments made on one species cannot, therefore, be made the basis of conclusions for other species; much less so for therapeutic use in man.

In this connection it is interesting to note that the author in conjunction with Herman and Levy has found that the analgesic power of a morphin-narcotin combination is much greater than the arithmetical sum of the analgesias produced by its constituents separately.[23]

Summary and Conclusions. 1. The comparative toxicity of morphin and narcophin was studied on various animals: pigs, fish, terrapins, mice, rats, guinea-pigs, rabbits, pigeons, cats, and dogs.

2. It was found that in general the toxicity of narcophin is about the same as the same weight of morphin.

3. Narcophin consists of one-third its weight of morphin meconate and two-thirds its weight of narcotin meconate. Inasmuch as the toxicity of narcotin is very low, we have here a distinct potentiation of the toxicity of morphin.

4. It is, therefore, not advisable to administer narcophin clinically in doses larger than those of morphin.

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[15] München. med. Wchnschr., 1914, p. 186.

[16] Therap. d. Gegen., 1914, p. 186.

[17] Deutsch. med. Wchnschr., 1914, p. 703.

[18] Therap. d. Gegenw., 1914, No. 3.

[19] Ibid., 1912, No. 11.

[20] München. med. Wchnschr., 1913, No. 2.

[21] Ibid., 1912, No. 28.

[22] Ibid.

[23] Jour. of Pharmacol. and Exp. Therap., 1916, viii, 1.

MULTIPLE PRIMARY INTRAVASCULAR HEMANGIO-ENDOTHELIOMATA OF THE OSSEOUS SYSTEM ASSOCIATED WITH THE SYMPTOMS OF MULTIPLE MYELOMATA—A LESION HITHERTO UNDESCRIBED.

By Douglas Symmers, M.D.,
ASSOCIATE PROFESSOR OF PATHOLOGY IN THE UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE; PATHOLOGIST TO BELLEVUE HOSPITAL AND TO ST. VINCENT'S HOSPITAL,
AND
Morgan Vance, M.D.,
PATHOLOGIST TO BELLEVUE HOSPITAL, NEW YORK.

(From the Department of Pathology of Bellevue and Allied Hospitals. Director, Dr. Charles Norris.)

We purpose to describe a lesion of the osseous system attended, by symptoms indistinguishable from those of the multiple myelomata and associated with histological features which combine with the clinical characteristics to form an apparently unknown disease.

Case Report.—The patient, a Russian machinist, aged forty-three years, was admitted to Bellevue Hospital complaining of severe pain in the left gluteal region. The pain extended upward to the tenth dorsal vertebra, but did not involve the lower extremities. The patient stated that the pain had grown progressively worse during the thirteen months previous to his admission to the hospital, that it was burning in character, continuous in point of time, and severest at night. Physical examination disclosed a small, indurated, exceedingly painful mass lying just to the left of the anus. The mass was attached to the tuberosity of the ischium. Roentgenographic examination showed irregularities in the periosteal outlines of the left ischium and signs of infiltration of the adjacent tissues. The corresponding hip joint was intact. In the course of the next two months the patient began to complain of tenderness and pains in the right lumbar region and buttock, in the upper part of the right thigh and in the axillary region of the right side. The manubrium sterni, the upper end of the right humerus, and the upper segment of the occipital bone were similarly affected. In the course of the succeeding five months two tender masses became palpable in the occiput and the movements of the left thigh and right arm grew to be exquisitely painful. Roentgenograms revealed complete absorption of the first rib on the right side and of the left ischium from the symphisis to the acetabulum and infiltration of the soft tissues of the vicinity, together with involvement of the upper end of the right humerus and fracture of the surgical neck. In the course of a few weeks there were signs of wide-spread destruction of the vertebræ. The patient, who was now anemic and emaciated, had to be kept under opiates for the relief of pain. Eventually he left Bellevue Hospital and died in another institution.

The urine was twice examined for Bence-Jones protein, with negative results.

There was nothing in the clinical manifestations or in the numerous roentgenograms to indicate visceral involvement, with the possible exception of a small cloudy area disclosed by one of the pictures taken of the lower lobe of the left lung.

In order to afford relief to the patient the tumor was curetted on several occasions, and, in this way, we were enabled to determine the microscopic changes in the skull, humerus, and ischium.

HISTOLOGY. The unit of the tumor is a thin-walled bloodvessel, lined by a single layer of flattened endothelial cells, the lumen distended by red blood corpuscles, the whole embedded in a stroma of poorly cellular fibrillar connective tissue arranged around spicules of bone. Here and there, however, the lining endothelium may be seen as a uniformly growing circumferential layer from 5 to 20 cells in depth, and from this point the process of proliferation may be followed through various stages leading to occlusion of the lumen by spindle-shaped tumor cells. In other cases the overgrowth of endothelium commences at the periphery of the vessel as one or more arm-like projections and the lumen is eventually occluded. An extraordinary histological feature consists in proliferation of the endothelium in such a way as to subdivide the vascular lumen into one or more compartments filled by red cells, obviously representing an attempt to form new vascular channels

SUMMARY. As far as we have been able to learn from a search of the literature on primary tumors of the bony system the lesion above described is unique. Zetkin,[1] for example, has called attention to a variety of so-called hemangio-endothelioma originating in the region of the diaphysis of the humerus. Not only was the origin a solitary one, but the histology is totally different from that of our tumor, consisting in alveoli of cuboidal cells of the epithelial type associated with numerous large, blood-filled channels embedded in connective tissue. The description of the histology reminds one of the adenocarcinomata or of the so-called hypernephromata. One of us (Symmers) has had an opportunity to study an apparently identical tumor springing from the humerus of a woman, aged forty-eight years, who, while riding in an automobile, and from a trivial cause, sustained a fracture of the bone. Microscopic examination of tissue removed by curettement (Dr. George D. Stewart) revealed a tumor composed of colloid-containing alveoli indistinguishable from those of the thyroid. There were definite indications of carcinomatous transformation. In addition the connective-tissue stroma supported innumerable large and small, thin-walled vascular channels packed by red blood cells and lined by a single layer of flattened endothelium. The question naturally arose as to whether the tumor represented carcinomatous metamorphosis of an aberrant thyroid in the humerus or a metastasis from a primary adenocarcinoma of the thyroid gland itself. Nearly three years have elapsed and the patient is perfectly well.

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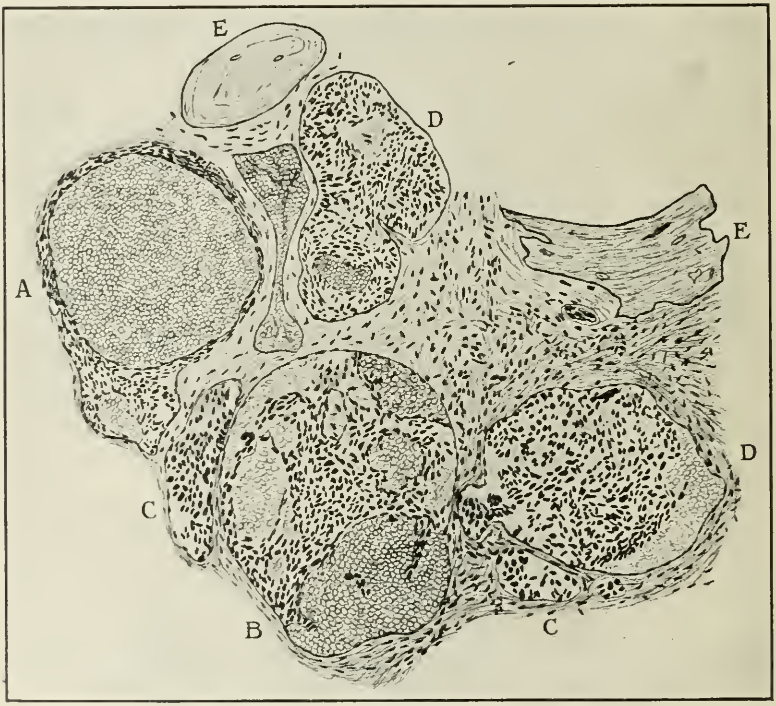
[1] Ann. d. Stadt. allg. Krankenh., München., 1910, xiv.



A, capillary distended by red blood cells and showing a circumferential layer of proliferating endothelium. At one end is a small subsidiary vascular channel lying in the endothelial layer; *B*, capillary vessel showing the presence of multiple subsidiary vascular channels; *C*, smaller vessels with their lumina almost completely occluded by proliferating endothelium; *D*, vessels distended by proliferating endothelial cells with only partial preservation of the lumen, which is occupied by red blood corpuscles; *E*, spicules of bone lying in a moderately cellular fibrillar connective tissue. (Drawn with Edinger's apparatus.)

Nauwerck[2] has described a so-called hyperplastic capillary angioma of the upper end of the femur. The tumor was composed of alveoli lined by cuboidal epithelial cells surrounding homogeneous plugs of colloid. In the supporting connective tissue were numbers of capillary vessels. From the histological description of the growth as well as from the illustration which accompanies Nauwerck's article it is obvious that he was dealing with a vascularized thyroid rest of the same type as that encountered in the humerus by both Zetkin and Symmers.

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[2] Virchows Archiv, cxi, p. 211.

The symptomatology of the condition which we have described above bears a close resemblance to that of the multiple myelomata—the occurrence of multiple primary tumors of the bones, particularly those with red marrow, including the skull, vertebræ, ischium, sternum, and ribs; excruciating pain and exquisite tenderness referable to the distribution of the osseous growths; apparent absence of visceral metastasis; regional infiltration of tissues following direct extension from the bone; spontaneous fracture; emaciation and anemia—all are symptoms highly suggestive of the myelomata. The resemblance is not vitiated by the absence of Bence-Jones protein in the urine, for not all cases of myelomata are attended by albumosuria and, moreover, the Bence-Jones protein has been demonstrated in the urine in lesions of the bony system other than myelomatosis.

Histologically the myeloma is a tumor springing from certain cytoblastic constituents of the bone marrow, and is oftenest composed of elements of the type of premyelocytes or of plasma cells. The tumor we have under consideration, however, presents totally different microscopic features in that it commences with overproduction of bloodvessels of the capillary variety and, as a result of continued proliferation of the lining endothelium, brings about distension of the vessel lumen and eventuates in its partial or complete occlusion by tumor cells. At the same time the tumor displays a remarkable tendency to produce subsidiary vascular channels within the lumen of the parent capillary.

THE DISTRIBUTION OF TETANUS TOXIN IN THE BODY.

By H. E. Robertson, A.M., M.D.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MINNESOTA.

(From the Pathological Institute, University of Freiburg in Br., Professor L. Aschoff, Director.)

It has been a matter of common experience ever since the laboratory study of tetanus began that when one injects a sufficient quantity of tetanus toxin into the muscles of the hindleg of a laboratory animal—*e. g.*, guinea-pig or rat—that after a varying period of incubation the injected leg will become stiff and outstretched. Then, generally, the toxin affects in succession the other muscles of the body, first those of the hindleg on the opposite side, next those of the back, and finally of the neck, thorax, and head. By this time convulsive seizures of increasing severity and with decreasing intervals have appeared, and at last, with asphyxia or exhaustion, death ends the scene. The convulsions are usually spontaneous, but may also be produced by sensory irritation, such as stroking, pinching, or a sudden noise. The inoculated limb, as a rule, remains stiff and outstretched until the moment of death, when it and the remaining muscles of the body become suddenly relaxed and softened, only to stiffen again after the rapid onset of *rigor mortis*.

If the toxin should be injected into other portions of the animal's body—*e. g.*, pleural cavity—instead of into the hindleg the gradual progression of the symptoms would not be so manifest and local or ascending tetanus[1] would appear. Either the muscles of the head and neck would be first attacked and then the remaining muscles in more or less regular succession, so-called tetanus descendens, or the order of the attack would be first local and then general without reference to the contiguity of the muscle groups or nerve centres, so-called mixed or general tetanus. Most of the laboratory animals, by inoculation into the muscles of an extremity, will exhibit local tetanus or tetanus ascendens. Tetanus in man or horses, on the contrary, is more apt to assume the form of tetanus descendens or general tetanus. No matter what may be the order of development, however, the symptoms are always so definitely similar and the clinical picture, as a whole, so unvarying that no argument is necessary to convince one of the specificity of the reaction.

That in natural infections by the tetanus bacillus this organism multiplies locally and elaborates a soluble toxin, which spreads throughout the body, is generally admitted; that the injection of an artificially prepared tetanus toxin into an animal's body in every way corresponds, in the principles governing its action, to the effect of a natural infection, hardly anyone will deny. But as to how this toxin spreads in the system, as to exactly what portions of the body are primarily attacked, and how this process is brought about, are questions which have led to long series of experiments, endless discussion, and many varied and opposing theories. It is not purposed here to discuss in detail all of the opinions which have been offered. For the present it will suffice to mention the more salient features of three important theories and discuss more extensively those which have a direct bearing on my own work and conclusions.

Among the former is the earlier work of Vaillard and Vincent, in which they expressed the belief that local tetanus was due to the direct action of tetanus toxin solely on the muscles themselves. Zupnik later developed and elaborated this assumption. He found that when he injected tetanus toxin into the subcutaneous tissues or into the nerve of an animal's foot at a point where the toxin could not come into contact with muscles the animals were affected by tetanus descendens and not localized tetanus. This latter form did not appear unless the toxin came into close association with muscular tissue, and when this took place those particular muscles were attacked by enduring spasmodic contractures which persisted for a long time and were not released by general anesthesia, curare, or cutting of the corresponding nerve trunks of the muscles. Zupnik attempted also to enervate completely the muscles of an extremity, and, by the injection of tetanus toxin into these muscles, he nevertheless obtained local tetanic spasms. He, therefore, concluded that the muscular phenomena of tetanus arose from direct intoxication of these muscles by the tetanus toxin.

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[1] For the accurate classification of these various types of tetanus (ascendens, descendens, and mixed) we are indebted to Zupnik.

This latter experiment of Zupnik's has been repeated, among others, by Sawamura and Permin, who were both able to show that when an animal's leg has been absolutely separated from all nerve connection with the spinal cord the muscles of that leg will always remain flaccid no matter whether the tetanus toxin be injected into these muscles or into some other part of the body. They believed that, due to faulty or incomplete enervation, Zupnik was able to obtain muscular spasms in the extremity so treated, because these muscles still retained some intact nerve fibers connecting them with the spinal cord. The other portion of Zupnik's evidence, namely, the enduring muscular contraction, requires more detailed consideration. As shown by experiment 8, when an animal dies from acute tetanus, following local injection of tetanus toxin, at the moment of death all the muscles of the body become soft, relaxed, and free from any stiffness or spasm.

Experiment 8.—Guinea-pig No. 3. Weight, 400 gms.

Jan. 29, 1915,	2.30 P.M.	Tetanus toxin,[2] 0.1 c.c. intraperitoneal.
Feb. 1, 1915,	8.00 A.M.	Right leg slightly stiff and extended.
Feb. 2, 1915,	8.00 A.M.	Right leg completely stiff. Beginning stiffness opposite leg.
Feb. 3, 1915,	9.00 A.M.	Rear portion of body entirely stiff and rigid. Spasms in muscles of back and neck.
	12.00 M.	All muscles of body except front legs affected. Respiration rapid.
	5.00 P.M.	Death (five days two and one-half hours). At moment of death entire body including hindquarters soft and freely movable.
	5.05 P.M.	Postmortem rigor, rapidly involving entire body.

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[2] For the tetanus toxin and antitoxin used in these experiments, I am indebted to the kindness of the Hoechst Farbwerke, Hoeschst, a. M.

This observation has been repeated many times in mice, rabbits, and rats as well as in guinea-pigs. That the same relaxing effect may follow the administration of certain drugs in the acute stages of tetanus is seen in experiment 94, a portion of whose protocol is given below.

Experiment No. 94.—Rabbit No. 5. Weight, 3000 gms.

Mar. 24, 1915,	10.00 A.M.	Tetanus toxin, 0.5 c.c. (right hindleg).
Mar. 25, 1915,	10.00 A.M.	No symptoms.
Mar. 26, 1915,	8.45 A.M.	Slight stiffness in right hindleg.
Mar. 26, 1915,	9.40 A.M.	$MgSO_4$ (25 per cent. sol.), 7 c.c. subcutaneous.
	10.10 A.M.	Stiffness entirely disappeared.
	6.00 P.M.	Right leg again stiff. $MgSO_4$ (25 per cent. sol.), 8 c.c. subcutaneous.
	6.30 P.M.	All stiffness disappeared.

This experience was repeated a number of times with this rabbit and with other animals, and demonstrated that under the influence of appropriate narcotics all local spasms in acute tetanus may be temporarily removed. The same fact has been shown many times by others in various ways, *e. g.*, by cutting the motor nerves, by ether or chloroform anesthesia, or by injections of cocain or curare, and leaves no doubt that the primary action of tetanus toxin is not on the muscles but is on the spinal cord.

Certain facts, however, which have been observed by almost every laboratory worker on tetanus and which formed a part of the evidence advanced by Zupnik in favor of his theory, remain to be explained. When one produces a local spasmodic contraction in an animal's muscles by injection of tetanus toxin and the animal lives long enough—*i.e.*, does not die with acute tetanus—this spasmodic contraction may become more or less permanent. The following protocol is an example of this frequently observed phenomenon:

Experiment 21.—Guinea-pig No. 17. Weight, 540 gms.

Feb. 10, 1915,	12.15 P.M.	Hoechst antitoxin, 1 c.c. (5.2 units[3]) intraperitoneal.
	2.15 P.M.	Tetanus toxin, 0.3 c.c. in muscle of right hindleg.
Feb. 11, 1915.		Right hindleg extended and stiff. Animal otherwise normal.
Feb. 12, 1915.		Stiffness of right leg more pronounced.
Feb. 13, 1915.		Entire right hindquarter stiff and board-like. No other muscles affected.
Feb. 22, 1915.		Leg atrophied. Foot swollen. Animal runs and eats.

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[3] German standard.

Mar. 1, 1915.	Weight, 470 gms. Appears thin. Otherwise the same.
Mar. 18, 1915.	Leg movable in foot portion. Swelling reduced. Weight, 500 gms.
April 23, 1915.	Leg movable in all portions. Slight stiffness at hip. Weight, 600 gms. (seventy-two days).

This same condition has also been repeatedly observed in rabbits and rats as well as in guinea-pigs. As has been shown by Goldscheider, Zupnik, Meyer and Ransom, Permin, and others, this sort of spasm does not disappear when the nerves are cut, or when narcotics or magnesium sulphate are given, or even after death. It is a long-enduring and almost inexhaustible stiffness which resists all attempts at passive motion, shows evidences of vascular and trophic alteration (atrophy and edema), and only after weeks and even months does it begin gradually to disappear. If the animal dies or is killed the changes found both grossly and microscopically are only those which might result from long and continuous non-use. Ribbert examined for Meyer and Ransom the spinal cord of a cat which had lived for five months with an unchanged tonic spasm of both hindlegs. He found that most of the ganglion cells of the anterior horns at this level showed degenerative changes. However, it appears probable that such changes are purely secondary. not representing in any way the primary action of the tetanus toxin on either the spinal cord or muscles. Just what combination of chemical changes must occur in order to convert a temporary and easily relaxable muscle spasm into an enduring one is not entirely clear. Gumprecht declared, "Dieser Starre der Muskeln ist nichts anderes als ein hochgradiges Ermuduengs-phaenomen, wie es den Physiologen vom electrischen Tetanus laengst bekannt ist." Meyer and Ransom suggest that such contractions represent a disturbance of the "muscle tonus" centres, which in their inexhaustibility and independence from volition are probably distinct from the motor centres. At any rate it becomes evident that the phenomenon cannot serve as proof for Zupnik's assertion.

The second of the three theories was advanced by Pochhammer who proposed to explain all local phenomena occurring in tetanus by the action of the toxin on the myelin sheaths of the peripheral nerves. According to him the tetanus toxin so alters the myelin that the normal insulation of the nerves is interrupted and "short circuits" may take place, especially in those nerve trunks which contain a mixture of sensory and motor fibers, whereby sensory stimuli pass directly across between the nerve bundles instead of being conducted along the normal reflex arc to the spinal cord. As a partial proof of this hypothesis he treated nerve trunks with ether, thus dissolving the lipoids in the myelin sheaths and producing an artificial "short circuit" which he asserted simulated that condition which occurs in tetanus. This latter experiment was repeated by Permin, who admits that when the nerves are so treated a stiffness of the corresponding limb results; but he concludes that this stiffness is not at all similar to that which is found in tetanus. Sawamura further calls attention to the fact that the direct injection of toxin into the substance of the spinal cord or brain will produce a fatal tetanus. Here a "short circuit" of the peripheral nerves can hardly enter into the question. Moreover, if the tetanus toxin has its primary and sole effect on the peripheral nerves, it becomes difficult to explain, not only the non-neutralizing actions of these nerves when mixed with toxin, as shown by Meyer and Ransom, but also the neutralizing action of the brain-and-cord-toxin mixtures, as demonstrated by Wassermann and Takaki. Not only has Pochhammer's theory received no substantial support from other workers, but it does not explain satisfactorily the various phenomena arising as the result of the inoculation of tetanus toxin.

The third theory received its chief support from Autokratow as well as Courmont and Doyon, who believed that the local spasm resulted from an intoxication of the peripheral sensory nerves alone, so that the supposedly more or less normal motor ganglion cells received intensified sensory impulses and reacted in a correspondingly intensified manner. They based their theory in large part upon the results of the well-known experiment (performed among others also by Goldscheider and Permin) in which, by cutting the posterior (sensory) lumbar nerve roots between the spinal ganglion and the cord, all tetanic spasms in the hindleg of an animal, in consequence of the injection of tetanus toxin, are at once released, if they have been present before the operation, or do not appear in this leg at all. In short, cutting the posterior nerve roots prevents or removes tetanus spasms in the muscles which are supplied by those nerves.

Other workers have endeavored in various ways to show the relation which the sensory nerves and centres bear to the general phenomena of tetanus. Sawamura cut as many as possible of the sensory nerves of the skin of a rabbit's hindleg, thereby producing complete anesthesia, and then injected tetanus toxin into the muscles of that leg. While tetanus symptoms finally appeared in the injected extremity, they were slower in developing and less severe than those caused by the same amount of toxin in an unoperated animal. Meyer and Ransom, on the other hand, injected tetanus toxin into purely sensory nerves such as the nervus infraorbitalis and saw not only an unusually prolonged incubation but also a marked diminution in the severity of the reaction. By still another and more striking experiment they were able to show that motor phenomena alone need not play the major role in the symptomatology of tetanus. After carefully exposing the spinal cord in the lumbar region they uncovered the posterior roots and injected tetanus toxin into one of these at a point between the lateral ganglion and the spinal cord. The animal developed a peculiar "sensory" type of tetanus, which they called "tetanus dolorosus" and which was characterized by the presence of a marked localized sensitiveness (Schmerzerregbarkeit), which was so extraordinarily pronounced that the slightest contact, even a light blowing on the skin of the affected area, led to a violent, apparently unbearable spasm of pain. These attacks also occurred in the form of paroxysms, interrupted by periods of comparative quiet. Owing to the fact that during these attacks the animal would bite at the affected area and make every effort to alleviate the acute pain, Meyer and Ransom concluded that the reaction represented "brain reflexes, *i. e.*, coördinated defensive movements (Abwehrbewegung)." Motor spasms or the usual muscular phenomena of tetanus were absent, the animal finally succumbing apparently only to exhaustion.

It thus appears clear that the sensory portion of the spinal cord and brain play some role in the production and maintenance of the typical spasms and convulsions of tetanus. One has only to observe closely the extreme sensitiveness to sensory stimuli which is exhibited by most tetanus patients to be convinced of the general application of this statement. To what extent, however, in the usual forms of tetanus there is a direct intoxication of the sensory nerve centres is by no means clear, and certainly it does not seem to be true that under ordinary circumstances the sensory nerves and those alone are affected. Referring again to the fundamental experiment in which is shown the effect on tetanus produced by section of the posterior nerve roots, may be mentioned the work on frogs by Hering, who cut the posterior roots during strychnin poisoning. So long as the motor neurons remained thereby isolated the animal showed no "strychnin convulsions," but on irritation of the central stump the state of increased excitability of the motor segment was at once manifest and typical tetanic spasms ensued. As strychnin admittedly affects the anterior horn cells of the spinal cord, this experiment would tend to show that also in tetanus the sensory fibers in the main merely serve to convey the stimuli necessary to set in operation the motor apparatus—in other words it demonstrates the physiological maxim that the motor ganglion cells do not act purely automatically.

According to Brunner, Goldscheider, Gumprecht, Marie and Morax, Stintzing, Meyer and Ransom, and Sawamura, the spasmodic contraction of the muscles seen in local tetanus results from the action of tetanus toxin on the anterior horn ganglion cells of that portion of the spinal cord governing the muscles of the affected extremity. In their opinion the toxin passes to these ganglion cells by way of the motor nerves, a theory with which most of the writers on experimental tetanus are today in full accord.

Meyer and Ransom, Marie and Morax, and Sawamura contend that this conduction of the toxin must take place along the axis-cylinders, or, as Meyer and Ransom say, "Das Gift muss also im Fibrillenplasma stroemen."

As proof of this contention, Marie and Morax injected tetanus toxin into the hindleg of a guinea-pig and after a definite lapse of time, by killing the animal, cutting out the sciatic nerves and inserting pieces of these under the skin of mice, were able to demonstrate the presence of toxin in the nerves of both legs, particularly in those of the inoculated leg. The blood of these guinea-pigs was also found toxic but not the muscles of the inoculated limb. This diffusion of toxin to the nerves, if they were normal, occurred within one and a half hours. If, however, they had been previously sectioned, twenty-four hours were necessary before any amount of toxin could be demonstrated in the peripheral or distal portion, while if one allowed six or more days to elapse, or until degenerative processes had had time to occur, no toxin at all could be shown to be present. The proximal or central portion of these cut nerves did not contain virus. Even when toxin was injected into other areas, such as the vitreous humor of the eye or the testicle, its presence could still be detected later in the sciatic nerves. If a nerve which had already absorbed toxin was cut this toxin rapidly disappeared from the central portion, and when toxin was injected into the lumbar swelling of the spinal cord it spread upward in the cord but not to the peripheral nerves. From these and similar experiments the authors concluded that the toxin was absorbed by the muscle nerve endings and passed centripetally to the spinal cord by way of the axis-cylinders and not either by nerve sheaths or by lymph channels.

This demonstration of tetanus toxin in the nerve trunks of peripheral nerves following intramuscular injections has been repeated and confirmed many times, among others by Pochhammer, Meyer and Ransom, Sawamura, and Permin. Also the retardation or even complete interruption in toxin absorption, which follows cutting the nerves of an injected limb, has been fully proved. For Meyer and Ransom these facts were sufficient grounds for postulating the condition of tetanus toxin in the axis-cylinders.

However, exception to this current view must be taken so long as it is not better supported. An important theoretical consideration in this connection must be mentioned. While, according to this theory, the toxin is conducted to the spinal cord and throughout the cord itself in the fibrillar structures of the axis-cylinders, both its chemical union and its toxic effect are supposed to take place in the protoplasm of the ganglion cells. This combined assumption is perhaps admissible, but, up to the present time, has not been demonstrated to be true for any other toxic substance. If the axis-cylinders really possess such a marked affinity for toxin that they can conduct this from the peripheral portions throughout the entire nervous system, the ultimate union with the protoplasm of the ganglion cells appears rather difficult to explain. Meyer and Ransom found that when normal sciatic nerves were cut and brought into contact with tetanus toxin *in vitro* they exhibited no particular power to fix the toxin. From this they concluded that the affinity between tetanus toxin and nerve substance was not the same kind as that which had been demonstrated by Wassermann and Takaki to exist between this toxin and brain or cord substance. But if the axis-cylinder theory holds true there must be some sort of affinity exerted by these structures for the toxin. Can this be denominated as a hitherto unknown "affinity to travel?" The axis-cylinders are an integral part of the ganglion cells, and if the protoplasm of these cells can remove the toxin from their own processes because of a special chemical affinity for it, it is difficult to understand why these cells cannot also take up toxin from the surrounding lymph.

In short, that tetanus toxin travels in the fibrillar substance of a nerve structure without being in any demonstrable manner bound by this substance, and that it is readily delivered to another element of these same structures (ganglion cell body) to form a firm chemical union, rather than that it travels in those paths natural and adapted for the passage to the cells of all substances in a fluid state—namely, in the lymph channels—from a purely theoretical stand-point does not appear to be sound doctrine. On the contrary, it is much easier to explain not only the natural manner of distribution of fluids to the tissues of the body, but also the facts in regard to the distribution of tetanus toxin to the central nervous system by supposing that this takes place by means of the lymph.

Apart from such theoretical considerations, one of the main arguments for toxin conduction by the axis-cylinders—namely, the delay or complete failure in toxin absorption after cutting the nerves—may as reasonably serve to support the conduction-by-lymph theory when attention is directed to the fact that, after cutting the nerves, the myelin sheaths of the peripheral fibers undergo degeneration and their disintegration products can be demonstrated histologically as more or less completely blocking the lymph channels. If it is true, as Gumprecht also asserted, that toxin absorption takes place through the lymph channels, then any paralysis of an extremity must diminish the rate of toxin absorption because of the failure of muscular activity. Also the longer the time which elapses after cutting the nerves, so much more complete will be the stoppage of the lymph channels until any further absoprtion becomes impossible. To the importance of these factors, Aschoff (through Rosenbach) has already called attention in connection with the absorption of adrenalin.

Permin removed the perineurium from a sciatic nerve and found that, after injection into its peripheral portion, toxin affected the body fully as rapidly as in a normal control animal. But in concluding from this experiment that the toxin must travel in the nerve substance itself and not in the lymph passages he overlooked the fact that countless other lymph channels, aside from those in the perineurium, course freely in the nerve trunks themselves.

Further evidence, however, remains to be explained. Meyer and Ransom, whose really brilliant work on experimental tetanus has done so much to clear up many mooted points in our knowledge of this disease, and who have been very active supporters of the "axis-cylinder conduction theory," carried out the following experiment: A rabbit was treated with tetanus toxin and highly immunized until a test of its blood showed that 1 c.c. held one-tenth antitoxin unit of 4,000,000 −Ms.[4] A large dose of tetanus toxin (5000 +Ms.) was injected subcutaneously without effect. Then in the left sciatic nerve a very small second dose of toxin (200 +Ms.) was injected and the animal on the following day showed severe tetanic spasms, particularly in the muscles of the left leg. A test of the blood removed at this time showed the antitoxin content unchanged. Tests of the cerebrospinal fluid and of the nerve lymph also showed the presence of antitoxin but "much less than the blood." Permin, who repeated and confirmed these results, also proved that a similar reaction can be obtained in an even simpler manner by injecting the antitoxin into the blood stream of a rabbit or dog and shortly after by an injection of toxin into the muscles of the hindleg, whereby a local tetanus ensues which is confined to the muscles of the inoculated leg. In my experiments on rats and guinea-pigs with the prophylactic application of antitoxin I have encountered the same phenomenon, namely, after the injection of concentrated toxin into the muscles of a passively immunized animal, local tetanus of the muscles of the injected leg would appear. Often this stiffness also affected the back muscles of the corresponding hindquarter, but, unless the dose of toxin was overwhelmingly large, this condition did not spread any further and did not endanger the life of the animal.

The possibility, then, must be admitted that tetanus toxin may travel along a nerve trunk to the spinal cord in the body of an actively or passively highly immunized animal, from which fact Meyer and Ransom concluded that the toxin in its passage along the nerves is not conducted in the lymph but, as quoted above,

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[4] The antitetanus serum unit, established by Behring and used to measure the potency of German serums, represents that amount which will protect one gram of mouse weight against 40,000,000 lethal doses of toxin. A unit lethal dose of toxin for 1 gram of mouse weight is denoted by the sign +Ms. The designation −Ms. refers to the amount of serum necessary to save 1 gram of mouse weight from the fatal effect of a unit lethal dose of toxin (1 +Ms.). Hence 1 A.E. (antitoxin einheiten) or unit represents 40,000,000 −Ms.

"Das Gift muss also im Fibrillenplasma stroemen." Permin from the same fact drew a similar conclusion, namely, that the experiment demonstrates that the nerve substance itself must be regarded as the conducting medium. This conclusion does not seem to be fully justified, and I believe that the facts can be better explained by the "lymph channel theory." Following injections of toxin, tetanic symptoms are produced simply because the tetanus toxin is concentrated enough to more than neutralize the antitoxin present and thereby can pass through the lymph channels to varying distances up the spinal cord before it is rendered harmless by the circulating antitoxin or is fixed by the nervous tissue.

When Meyer and Ransom and also Sawamura injected tetanus antitoxin into a nerve trunk they found that this particular nerve and its corresponding nerve segment were fully protected from the action of the following injection of tetanus toxin, no matter whether this toxin was injected directly into the same nerve or into some neutral area. In other words, they provided antitoxin in sufficient local concentration to neutralize an equally or less locally concentrated toxin.

Ransom has shown that in whatever manner either tetanus toxin or antitoxin may be injected into the body, they both shortly appear in the blood stream and thence in the lymph. The antitoxin apparently remains in the blood and the lymph until its final disappearance from the body, while the toxin is largely taken up by the nerves, conveyed to the cord and brain, and there fixed in the protoplasm of the ganglion cells. However, it seems well established that the lymph channels of the body, apart from the site of injection, never contain antitoxin in very concentrated amounts and this appears to be equally true of the lymph spaces of the central nervous system. Indeed, Meyer and Ransom assert that antitoxin does not enter the central nervous system by way of the blood and lymph streams, an opinion which perhaps expresses too strongly the *paucity of concentrated antitoxin* in that part of the body for later in the same paper (p. 413), in discussing the researches of Roux and Borrel, who were able to produce tetanus in highly passively and also actively immunized dogs by injections of toxin into the cerebral substance, Meyer and Ransom suggested that "the toxin concentrated at the site of injection could not be at once neutralized by the antitoxin which was certainly present in the centres although in low concentration, and consequently, enough time elapsed in which to poison the nerve cells before sufficient additional antitoxin-laden blood appeared; we have to deal, then, with a regional difference of concentration." This condition of affairs also maintains when concentrated toxin is injected in or near a nerve trunk, and the facts brought forth in this connection cannot serve as arguments in favor of the conduction of tetanus toxin along the axis-cylinders.

On the contrary, the evidence so far presented by the numerous workers is distinctly in favor of the theory which designates the lymph channels as the natural medium of exchange for fluids between the different portions of the body, including the central nervous system.

The chief supporters of this latter view have been Gumprecht and Stintzing, the last named having reported the presence of tatanus toxin in the cerebrospinal fluid of two human cases of tetanus. This finding has not been sufficiently confirmed either in cases in men[5] or by animal experimentation (Ransom). I have tested on white mice the cerebrospinal fluid from two severe fatal cases of tetanus and was unable to prove the presence of tetanus toxin. Gumprecht's conclusions, on the other hand, were based on purely experimental grounds. He injected tetanus toxin into the subdural space of the lumbar cord and found that tetanus appeared first in that extremity corresponding to the side on which the injection was made. He called attention to the injection experiments of Key and Retzius, who, by means of Berlin blue and gelatin (Richardson's blue), found that not only are the peripheral nerves and spinal cord full of intercommunicating lymph channels, so rich that even each individual fiber is surrounded, but also that everywhere along the cord are free communications with the subarachnoidal lymph spaces, which spaces in turn freely open into the lymph channels of the perineurium. Therefore Gumprecht stated that "after injection into the hindleg the toxin readily ascends in the numerous lymph spaces of the nerves and on reaching the spinal cord is diffused both up and down (in the cord)."

I have repeated in part Key and Retizius's injection experiments, and have found that by injecting the sciatic nerve a short distance below the spinal ganglion with Richardson's blue the fluid passes freely through the ganglion toward the cord along the motor roots. The lymph channels of the sensory roots are either not injected at all or injected with difficulty by this means. . Neither does there appear to be such free communication between the endoneural spaces and the subarachnoid spaces as Key and Retizius indicated, for when the injecting needle is kept in the central portions of the nerves the fluid mass remains within the nerve sheaths and does not invade the arachnoid unless rupture from undue force occurs. The point is of some importance, as it not only explains why tetanus toxin under ordinary circumstances does not pass into the cerebrospinal fluid, and thus why Stintzing's observations have not been fully confirmed, but also it perhaps gives a hint as to why the usual type of tetanus is a motor tetanus and not "tetanus dolorosus," as obtained by Meyer and Ransom when they injected toxin into the posterior roots. In other words, the toxin by following the lymph channels passes first to the motor side of the cord.

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[5] While most workers report uniformly negative results it should be noted that Permin claims to have demonstrated tetanus toxin in the cerebrospinal fluid of five human cases.

Meyer and Ransom repeated Gumprecht's experiment of injecting tetanus toxin into the subdural spaces and confirmed his results. However, while Gumprecht believed that the toxin passed directly by means of the perivascular spaces to that portion of the spinal cord with which it first came into contact, on the other hand, Meyer and Ransom concluded that it was first absorbed into the blood stream, taken up by the peripheral nerves, and thus conveyed in the usual manner to the spinal cord, where that part which had been injured by the injection, a *locus minoris resistentiae*, would be the first affected. This hypothetic injury, they believed, was impossible to avoid.

It is necessary to note here an experiment of Permin, whose views, as stated, are in full accord with those of Meyer and Ransom. After injecting tetanus toxin into the muscles of the hindlegs of rabbits, and at the same time antitoxin into the blood stream (to prevent general tetanus), he injected antitoxin intraspinally at varying intervals of time. Such injections had to be made within at least four hours after the injection of the toxin in order to prevent the outbreak of a local tetanus. Permin does not explain how this result was accomplished, but it is reasonable to suppose that the antitoxin passes into the lymph channels of the nerve roots and there neutralizes the ascending toxin which must also be in the nerve lymph. From this experiment he rightly concludes that the conduction of toxin in the nerves must proceed with extraordinary rapidity (p. 24), a fact which is well explained by the rapid movement of lymph in the nerve sheaths. Pochhammer, in support of his theory after injecting tetanus toxin into the leg muscles of rabbits, killed the animals, cut out the corresponding sciatic nerves, and, dividing them into three parts, placed each piece under the skin of mice. He found that the peripheral portions of these nerves always held more toxin than the central portions. Sawamura fully confirmed these observations, which also agree with Meyer and Ransom's experiment, in which they found that after cutting a nerve holding toxin this toxin rapidly disappeared from the central or proximal end. While the conclusions derived from these various experiments were different and even contradictory, the results seem to be in full accord with the theory of tetanus toxin conduction by nerve lymph channels. This conduction naturally is slower in the finely divided distal nerve branches, but as the larger nerve trunks are reached and the lymph finds wider spaces through which to travel, the speed is accelerated and not only does the toxin spread faster but it is more diluted by the inflowing lymph currents and can thus more readily be neutralized by the less concentrated antitoxin. It is not possible to explain all these facts by the axis-cylinder conduction theory.

One further expriement was suggested by Professor Aschoff which might throw more light on the subject. This experiment is based upon the theory that if tetanus toxin is conveyed by the axis-cylinders of the peripheral nerves to the spinal cord, it must also pass up the cord by the same means, while if conveyed to the cord by the lymph channels it must likewise spread by means of the lymph channels. But the spreading of toxin by means of the lymph channels can be prevented by a previous administration of antitoxin, which same, on the other hand, should not prevent the passage of toxin along the axis-cylinders. Hence, if toxin be injected into the lower end of the spinal-cord substance of a passively immunized animal, the manner in which the animal reacts should furnish decisive evidence in favor of one or the other contention. The protocols of these experiments are as follows:

Guinea-pig No. 38. Weight, 350 gms.

April 20, 1915. 1 c.c. tetanus antitoxin, subcutaneous. Twenty-four hours later, under ether anesthesia, the lower portion of the back was prepared for a surgical operation. Through a 5 cm. longitudinal skin incision the fascia and muscles were cut away and by sharp-pointed scissors the spinous processes and posterior portions of the lowest lumbar and upper sacral vertebræ removed, thus exposing the terminal portion of the sacral and lower lumbar cord. Into this exposed cord by means of a fine needle, inserted as far up as possible, 0.1 c.c. of tetanus toxin slowly injected.[6] The needle left in place a few minutes and then slowly removed. Muscles and fascia then carefully brought together by sutures, the skin sewed and the wound covered with an iodoform-collodion dressing. One-half hour later the guinea-pig runs about and is apparently normal in all its movements. On following day there was some distention of bladder by retained urine, which is relieved by gentle pressure on lower abdomen. No tetanic symptoms. Animal eats and runs about in normal manner. Forty-eight hours later the condition was the same. Bladder paralysis has disappeared. Ninety-six hours later there were no symptoms of tetanus or infection of wound.

Control. Rat No. 59. Weight, about 150 gms. Tetanus toxin, 0.003 c.c. in left hindleg. Forty-eight hours later there was marked local tetanus in the left hindleg.

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[6] As can be seen by the control experiment this dose was about fourteen times that which would produce tetanus symptoms in the same weight of rat body.

Guinea-pig No. 25.

Mar. 26, 1915. Antitoxin, 0.4 in left hindleg. Five hours later, antitoxin, 0.1 c.c. again in left hindleg.

Mar. 27, 1915. Spinal column and outer end of spinal canal exposed through opening in dura. Toxin, 0.02 c.c. injected into canal.

Mar. 28, 1915. General condition good. Runs about and eats. Bladder and rectum paralyzed.

Mar. 29, 1915. Condition the same. No signs of tetanus.

Mar. 31, 1915. Weaker. Animal killed by ether. No evidence of tetanus. Autopsy: bladder markedly distended. Kidneys show hydronephrosis. Wound clean.

Guinea-pig No. 39. Weight, 500 gms; pregnant.

April 20, 1915. Tetanus antitoxin, 1 c.c., subcutaneous.

April 27, 1915. Injection repeated.

April 28, 1915. The same operation as in No. 38 only slightly higher up and 0.15 c.c. toxin injected into the spinal cord. Animal recovered from operation. Bladder paralyzed. (Control rat died at end of five days). Animal became weaker and without showing the slightest symptom of tetanus was killed after six days. Autopsy showed dead fœti. Wound clean.

Guinea-pig No. 41.

May 6, 1915, 8.00 A.M. Tetanus antitoxin, 1 c.c. in left hindleg.

10.30 A.M. Same operation on spinal column as described above and 0.2 c.c. tetanus toxin injected into the spinal cord.

11.00 A.M. Animal recovered from operation. Eats and runs about.

6.00 P.M. Slight stiffness in hindleg.

May 7, 1915, 10.00 A.M. No further evidences of tetanus. Twenty-six hours after operation animal died suddenly.

12.50 P.M. Autopsy: hemorrhages and pneumonia in both lungs. Spinal cord swollen and moist.

Guinea-pig No. 42.

May 10, 1915. 1 c.c. tetanus antitoxin, subcutaneous. After twenty-four hours, operation as described above and injection of 0.2 c.c. tetanus toxin. No trace of paralysis or tetanus at any time. Control rat dead from typical tetanus after two and one-half days.

These experiments demonstrate that by the injection of tetanus toxin into the lower end of the spinal cord of a passively immunized animal, this toxin, even in doses which were sufficient to provoke symptoms in control animals, neither produced any marked local effect nor advanced in the spinal cord toward the more sensitive centres of the medulla, in short, that it was not taken up by the axis-cylinders but was prevented by antitoxin from spreading along its natural and customary route, namely, the lymph channels. The experiment moreover confirms in another manner the observation already noted on the occurrence of local tetanus when toxin is injected into the sciatic nerve or into the muscles of an animal's hindleg. In the presence of antitoxin in the system, tetanus toxin, whether injected into the hindleg or into the lower end of the cord does not travel far in the cord, because manifestly as it become more diluted, the antitoxin which is present in the lymph spaces of the spinal cord as well as in the lymph channels of the nerves has an opportunity to neutralize fully the less concentrated toxin and thus protect the portion of the nervous system lying above. The efficiency of this protection is exactly in proportion to the concentration of the antitoxin as compared with that of the toxin.

The objection raised by Permin that if toxin is transported in the lymph spaces of the spinal cord it would be difficult to explain the marked local tetanus which occurs when the leg of an immunized animal has been injected with toxin, does not assume so much weight when we take into consideration the fact that the concentrated toxin passes to the cord by definite lymph channels which are more or less closed until they reach the widely spreading spaces of the cord itself.

I have developed this theme at some length, believing it to be not only of theoretical but also of more than ordinary practical importance. Prophylactic or therapeutic methods in the rational treatment of any disease must be based, as far as possible, upon our knowledge of the causes of this disease and the manner of operation of these causes in the body. Hence in tetanus: if we assume that the path of attack of the toxin in the central nervous system is the axis-cylinders of the cerebrospinal nerves, then our plans for both prevention and treatment should be considerably different from those which should be adopted, if we believed the toxin to be distributed to the ganglion cells by the lymph stream. Terminal nerve fibrils are abundant over especially the entire tegumentary and muscular portions of the body. If they possess for tetanus toxin a "conductive affinity," then, in spite of all we may hope to accomplish even by prophylaxis, without complete enervation of the local area where the toxin is elaborated, the absorption by these fibrils of toxin before it can possibly be neutralized and the subsequent intoxication of corresponding nerve centres cannot be prevented by any means which, at present, is at our command. Antitoxin, admittedly, does not travel in the nerve fibrils but in the lymph channels, and hence the passage of toxin, on the basis of the above theory, cannot be interrupted.

However, it would appear more reasonable to assume that tetanus toxins, just as other poisons, pass throughout the body exclusively by the blood and lymph streams and, theoretically, may be neutralized by antitoxin and at any stage in this passage before the final and comparatively indissoluble union with the ganglion cells occurs. The practical difficulties associated with neutralizing, by injections of antitetanus serum, the toxin already in the nerve trunks, in cases of outbroken tetanus, have been discussed in a previous paper.[7] But assuming the lymph-conduction theory to be true, these problems, however practically insurmountable they may be at the present time, are still capable theoretically of solution, and no doubt in the future some method may be found for the immediate protection of threatened nerve cells and perhaps even the saving of those already attacked. At least the situation is by no means hopeless.

In this connection may be seen the rationality of Behring's early endeavors to obtain a highly potent antitetanus serum, a serum so concentrated that, diluted as it must be by all the tissue fluids of the body, when it comes into contact with toxin it shall possess enough "neutralizing mass" to meet and overcomes this toxin, before the vital centres can be affected.

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STUDIES ON A CASE OF IDIOPATHIC PURPURA HEMORRHAGICA.

By George R. Minot, M.D.,

ASSISTANT IN MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT IN THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON.

(From the Medical Service of the Massachusetts General Hospital.)

Purpura hemorrhagica is a condition that is characterized in its severer forms by hemorrhage from the mucous membranes, petechiæ or ecchymoses of the skin, a markedly reduced platelet count, a much prolonged bleeding time and non-retractile blood clot. A normal or somewhat delayed coagulation time occurs.

In its milder form there may be but ecchymoses following injury or excessive bleeding from some local cause; the other characteristics mentioned above, though present, are not so extreme. In this country, Duke[1] [2] especially has studied this condition.

This form of purpura, though often not clearly differentiated in the literature from other types of purpura and hemorrhagic disease, can be easily distinguished from them, because in these conditions there is no reduction of the platelet count.

Purpura hemorrhagica may occur as an idiopathic disease, though more frequently perhaps as a symptom complicating various diseases, especially aplastic anemia, leukemia, tuberculosis, nephritis, etc. A congenital idiopathic type exists.

Case Report. Various studies on a case of the idiopathic type which died in spite of eleven transfusions of blood are presented below. A summary of the case which entered the hospital February 16, 1915, is as follows:

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[1] Arch. Int. Med., 1912, x, 445.

[2] Jour. Am. Med. Assn., 1910, lv, 1185.

Number 200344. Russian Jewess; unmarried; aged eighteen years. Lived in Massachusetts twelve years. Her only work has been studying at school. Her home in Salem is clean, well ventilated, and in a good locality.

Family History. Entirely negative. No known exposure to tuberculosis.

Past History. She has always been strong and well except for mumps, measles, and diphtheria, which diseases she had as a small child. Her habits and bodily functions have been normal. Three weeks before her illness began she moved to a new house, owing to the Salem fire. This caused no undue excitement. Except for this, nothing unusual has happened to her in the past two years.

Present Illness. In July, 1914, she first noticed a few small, pea-sized, well-defined red spots on her feet and ankles which turned darker in color. Later the spots sometimes appeared as larger red areas or areas of bruised flesh. Since July she has never been free of such spots on her body, some disappearing as others reappeared, being more evident some weeks than others.

By degrees the spots appeared higher and higher on her body, reaching her face about a month before entrance, never, however, being marked on the abdomen. No bleeding occurred from the mucous membranes until about a week before entrance, but in the past week blood has been more or less continually oozing from the gums. During the past three days there has been a dull pain in the left hip, and today in the right jaw. She considers her general health good. There have been no systemic symptoms except that her menstrual periods have become more painful with an excessive amount of flow. A period is now present.

Physical Examination. A well-developed and nourished girl appearing distinctly pale. Scattered all over the body, but least on the trunk are very many discrete, rarely confluent hemorrhagic macular areas 1 to 5 mm. in diameter, especially prominent over the tibiæ, which are somewhat tender to pressure. The scleræ of both eyes show several pin-point hemorrhagic spots. The mucous membranes of the mouth and tongue show numerous discrete hemorrhagic areas. There is a large hematoma in the soft palate. A few bleeding-points occur in the gums about the teeth. Excessive menstrual flow.

Roentgenological Examination (Dr. Holmes). Teeth and sinuses: "Question of pus about right lateral incisor. Small right frontal sinus. No pus." Tibiæ: "Slight cortical thickening, otherwise negative."

Except for the above the physical examination was entirely negative. The abnormal laboratory findings will be discussed below.

Summary of Clinical Notes. February 23. The purpuric spots have nearly all gone. Bleeding from vagina and gums stopped three days ago.

February 28. A fresh crop of spots have appeared over skin and mucosa of mouth. Bleeding recurs from gums and vagina.

March 5. Spots have been increasing over arms and legs, increased profuse bleeding from gums, slight increase from vagina. Positive guaiac test on stool.

March 8. First transfusion, 300 c.c. of blood. Bleeding not checked.

March 10. Guaiac test on stool negative. Spots on skin fading. Less bleeding from gums and vagina.

March 11. Second transfusion, 900 c.c. of blood.

March 12. No new skin lesions. Distinctly less bleeding. Pelvis full of clots. Temperature rising.

March 19. There has been no further bleeding from gums and no new skin lesions; bleeding from vagina, however, has been persistent, though not severe.

March 23. General abdominal pain; no spasm. Vomiting two to three times a day in past two days. Small amounts of blood in vomitus. In past four days increasing bleeding from gums and vagina.

March 24. Third transfusion, 900 c.c. of blood. Less bleeding tonight.

March 26. Slight bleeding from gums. Less from vagina since transfusion.

April 2. Increased vaginal bleeding, daily. Severe bleeding from gums recurs today, there having been none for four days. Small amount of blood in catheter specimen of urine. Very rare minute punctate hemorrhages in skin of arms and legs. Patient appears much sicker. Fourth transfusion, 1000 c.c. of blood.

April 6. The only bleeding since the last transfusion has been a slight amount from the vagina. Tonight, however, the gums began to bleed again. The vaginal bleeding doubled in amount.

April 12. Continued increasing bleeding from gums, with petechiæ on lips. Vaginal bleeding profuse. No skin lesions. Fifth transfusion, 900 c.c. of blood.

April 20. Vaginal examination negative except for clots in vagina.

April 29. Since the last transfusion she has felt better and there had been no bleeding of any sort except for very slight bleeding of gums on April 21, a very few small purpuric spots on April 24, and upon sitting up in a chair on April 27, numerous small petechiæ appeared on the lower legs.

May 3. In past three days slight bleeding from gums. Few small purpuric spots appear on back of neck and legs today. Vaginal bleeding commences again.

May 18. There has been continued and increasing bleeding from gums and vagina. Blood appears in urine. Generalized purpuric skin lesions, distinctly fewer and smaller than on entrance, appeared May 11. A few small new spots have appeared each day since. Sixth transfusion, 900 c.c. of blood. Marked bleeding from wound.

May 23. Daily increasing amount of bleeding from gums and vagina with persistent hematuria. No new skin lesions. In general, appears sicker. Seventh transfusion, 900 c.c. of blood. In the evening following this transfusion the bleeding from the gums and kidneys stopped but persistent vaginal flow continued.

May 26. Hemorrhage into right retina. Few hemorrhagic spots in both scleræ. No bleeding from gums. Excessive bleeding from vagina. A little bleeding from kidneys.

May 27. Eighth transfusion, about 700 c.c. of blood.

May 29. Very little bleeding from any source. Patient transferred to surgical service, and Dr. Davis did a hysterectomy with double salpingoöphorectomy followed by the ninth transfusion of blood, 1100 c.c. The ovaries were cystic, containing hemorrhagic fluid. Dr. W. F. Whitney reports "hyperplastic endometritis."

June 1. Since operation, though gradually diminishing, there has been severe oozing from both abdominal and transfusion wounds, though dressings reinforced, they are repeatedly and frequently stained through. Very little bleeding from vagina. None from gums and no skin lesions.

June 3. Bleeding from gums recurs. Another retinal hemorrhage. Few petechiæ about lips. Dysuria with large amount of blood in catheter specimen of urine. No bleeding from operation wounds.

June 11. Continued persistent bleeding daily from kidneys and mucosa of mouth. Slight bleeding from vagina. Tenth transfusion, 1000 c.c. of blood.

June 15. Since last transfusion no bleeding from vagina. Though distinctly less, some from gums and kidneys. No skin lesions.

June 25. Her general condition is better, still there has continued daily hematuria which though perhaps diminishing is plentiful today. "Coagulen" 5 gm. subpectorally.

June 26. No hematuria.

June 28. Hematuria reappears.

June 30. Five grams of "coagulen" subpectorally.

July 3. There has been no further hematuria or bleeding. Eleventh transfusion, 800 c.c. of blood.

July 4. In the past two weeks there has been a distinct improvement. Patient discharged today.

During July the patient was not seen, but stated that at times, though she had slight bleeding from her gums, had seen no blood in her urine, and but occasionally a small purpuric spot on her skin. In early August she felt weaker, had perhaps some blood in her urine, and had bleeding from her gums. The patient was last seen August 14, when she had numerous purpuric lesions scattered over her arms and legs and mucosæ, with bleeding from her gums but no hematuria. Death occurred about August 29. There was no autopsy. From the history given by the family it seems that she gradually grew weaker without any extensive bleeding, and that possibly death may have been caused by a cerebral hemorrhage.

Temperature, Pulse and Respiration. During the patient's stay in the hospital, the temperature usually fluctuated daily 1° or so.

From entrance, February 16, until March 1 the temperature remained between 99° and 98°. Between March 1 and March 16, between 99° and 101°. A temperature between 102° and 104° occurred during the next week, and from then until April 15 a temperature of between 101° and 102° and 99° was seen. In the next two and a half weeks, 98° to 99° then fluctuating between 98° and 100.5° until June 5. From June 5 to June 26 fluctuations of often 2° a day occurred between 100° and 103°. From then until discharge, July 4, a gradual drop to 98° to 99° occurred.

The pulse followed the temperature, being 80 to 90 in the first weeks with the temperature 98° to 99°, but tended, as the disease progressed, to reach a higher level of about 105 with the same temperature. With the temperature 99° to 101° the pulse was 100 to 120, often rising to 140 or even 150 when the temperature was above 101°.

The respirations averaged about 22, reaching 26 to 30 with the highest temperature.

Laboratory Examinations. *Urine:* The urine was examined frequently while the patient was in the hospital and was negative except for the findings given below. There was nearly always a very slight trace of albumin, with larger amounts when blood was present. Occasionally there was a granular cast. In March a few red cells were occasionally found in catheter specimens. From May 17 to June 26 red cells were nearly always present, often in large numbers. Cultures were negative.

Stool: Examinations in March, April and May were negative except for a slight positive guaiac test March 4 and 23.

Blood Cultures: February 22, March 20, and April 15 showed no growth.

Wassermann reaction on blood, negative.

The Blood: (The routine red and white counts in most instances were made by the house officers, especially Dr. Colwell, as were also the smears, which were examined later by me.)

Red counts were made about every four days, at times more often. At entrance the count was 2,104,000 and remained at about this level until after the second transfusion on March 11, when it rose to 2,784,000, falling at first rapidly, then gradually to 920,000 on March 24. On this latter date after the third transfusion the count rose to 1,947,000, only to fall to 800,000 before the fourth transfusion on April 2, after which it rose to 2,100,000. On April 12 the count was 808,000 but rose on this day after the fifth transfusion to 2,320,000 and to 3,020,000 on April 28, falling to 2,440,000 May 17. Small rises and rapid falls followed the transfusions of May 18, 23, and 27, so that the count was 1,800,000 after the eighth transfusion which took place May 27. After the ninth transfusion, May 29, the count was 3,664,000. A fall to 1,096,000 occurred by June 11, on which day the tenth transfusion was done and the count rose to 2,664,000 falling by July 3 to 1,424,000, and after the eleventh transfusion on this day to 3,184,000. On August 11 the count was 2,720,000.

The hemoglobin varied from 65 per cent. to 20 per cent., fluctuating with the red count so that the color index was usually below 1, though sometimes 1. After transfusion the hemoglobin rose relatively more than the red count.

White counts were made frequently. On February 17 the white count was 15,600, on February 21, 7000 and remained at about this latter figure until March 12 when it rose to 11,000 and to 16,200, March 16, falling to 10,000 on March 20. On March 29 it was 22,000, becoming 7000 April 2. During April and May it was always above 6000, usually about 9000 to 11,000. June 16 and 30 the count was 8000 and 16,000 respectively. On August 11, 6400.

Study of Stained Smears and Differential Count. Smears stained by Wright's stain were studied about every ten days. The fresh blood stained with brilliant cresyl blue was studied when the reticulated cells were counted. (See below.)

The red cells always showed considerable achromia, some poikilocytosis most marked when the red count was lowest. There was a tendency to diminution in size. Polychromatophilic cells never appeared in large numbers, though more numerous after March 13. Rarely were any stippled cells found. In counting 100 white cells, two normoblasts were found April 12 and August 11 and one on March 15. Very rarely was a normoblast seen at other times, never megaloblasts.

Platelets were absent in the smears or exceedingly rare.

The white cells showed no striking abnormality. The percentage of polymorphonuclear neutrophiles varied from 72 to 54 per cent., and the small lymphocytes from 21 to 39 per cent. A higher percentage of polymorphonuclears occurring with the higher white counts, though often some of the lower counts gave 60 to 65 per cent. of polymorphonuclears. The large lymphocytes and mononuclears varied from 2 per cent. to 7 per cent., and the transitionals from 1 per cent. to 5 per cent. Mast cells were rarely found. Usually there were no eosinophiles seen, though they rarely formed 1 per cent. or 2 per cent. On March 15, April 12, and May 17 a single myelocyte was found on searching several smears.

Exceedingly rarely was there a Howell-Jolly body seen.

The Arneth picture remained normal or showed a slight shift to the left, not as has been found in pernicious anemia by Briggs[3] a shift to the right.

TREATMENT OF THE CASE. While the patient was in the hospital she was in bed except from April 27 to April 30, eating most of the time plentifully of a generous mixed diet. At times she received small doses of simple remedies to alleviate headache, nausea, constipation, etc.

Her chief treatment consisted of repeated transfusions by Dr. Leland from a donor belonging to the same isoagglutinin group[4] (Group IV). The transfusions were done by the indirect method except the second one. The effect of the transfusions may be seen by following the clinical notes. When the situation seemed hopeless the pelvic organs[5] were removed; though checking the hemorrhage through the vagina, this did not affect the disease.

In the literature there are instances in which transfusion has apparently cured purpura hemorrhagica, but also other instances where it has failed, and our case serves as an example to show that even in spite of persistent transfusion the outcome may be fatal. On the contrary, persistent transfusion may restore the patient to health, as was seen in a case of benzol poisoning[6] with symptomatic purpura hemorrhagica. The clinical picture, for about six weeks during which time five transfusions were done, was very similar to our present case. This case of benzol poisoning in contrast to ours then began to slowly but persistently improve.

On May 21 our patient received a massive dose of Roentgen rays, but this did not result in any benefit.

Locally for the bleeding from the gums and vagina at various times, solutions of different astringents were tried, but without any very striking effect.

Thromboplastic substances accelerate the coagulation of the blood and may perhaps be of value in checking hemorrhage. Two such substances were tried on this patient; "kephalin"[7] (the active thromboplastic substance) from sheeps' brains and "coagulen,"[8] a substance derived from blood platelets. Tests made *in vitro* showed that kephalin has a slightly stronger thromboplastic action than coagulen. During May, solutions of kephalin were applied to the gums and also sprayed into the vagina. This substance acted better than any astringents, it checked bleeding by allowing clots to form rapidly. However, the effect was but temporary, lasting only until the clot was loosened mechanically or by blood exuding behind it. Attempts were made to have the patient take kephalin by mouth, but after a few doses it proved so nauseating to her that it was not continued.

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[3] AM. JOUR. MED. SC., 1914, cxlviii, 143.

[4] Moss, Johns Hopkins Hosp. Bull., 1910, xxi, 63.

[5] A case is mentioned by Ottenberg and Libman, AM. JOUR. MED. SC., 1915, cl, 36, where removal of the uterus was beneficial.

[6] Minot, Denny and Davis, Arch. Int. Med., 1916, xvii, 101.

[7] "Kephalin," a wax-like substance was prepared according to Howell's method (Am. Jour. Physiol., 1912, xxi, 1), and dissolved in cold water when desired for use.

[8] "Coagulen" is an expensive commercial preparation made by the Gesellschaft f Chemische Industrie in Basel and sold under the trade name of "Coagulen Ciba," or "Coagulen Kocher Fonio."

Coagulen, which Fonio[9] has enthusiastically recommended for its ability to check any sort of hemorrhage or hemorrhagic disease, was given (5 gm. in 300 c.c. of salt solution subpectorally) June 25 and 30, followed by improvement in the patient's condition. Though improvement occurred coincident with the giving of coagulen, we feel that it was by no means wholly due to this substance. In some conditions, however, thromboplastic substances are of very distinct benefit for controlling hemorrhage.

THE PLATELETS. Denys's[10] observation in 1887 that the blood platelets are reduced in purpura hemorrhagica has been verified numerous times.

The blood platelets of our patient were counted by Wright and Kinnicutt's[11] method.[12] Daily counts were made during the first ten days and sometimes after this; more often counts were made every few days except in June. The count was always abnormally low, lowest at the times of the greatest bleeding, as Duke[13] found in his cases.

On entrance, February 17, the count was 1200, at which time the bleeding was severe. As the bleeding checked the count rose to 10,000 February 20 and to 26,000 February 24. With the recurrence of bleeding the count fell and remained about 1000, with a very slight rise after the transfusion of March 8. Before transfusion March 11 the count was 8000 and the following day, when there was distinctly less bleeding it was 70,000. A gradual fall took place in the following days, reaching 22,000 March 17 and 8000 March 20, when the bleeding again increased and the previous low level of 1 to 2000 was reached on March 23; after the transfusion on March 24 the count rose to 42,000, and there was less bleeding. In five days the count fell to 2000, bleeding increased, and the count remained at this level until after the fourth transfusion April 2, when it reached 118,000 and the bleeding was checked. A rapid fall to 4000 occurred in the next four days, when the bleeding increased markedly. A temporary rise to 26,000 occurred on April 7, without any change in the amount of bleeding, which was followed by a fall in the count. Following the fifth transfusion, April 12, the count rose to 120,000, reaching 75,000

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[9] Mitt. aus dem Grenz. der Med. u. Chir., 1914, xxvii, 642.

[10] La Cellule, 1887, vol. iii.

[11] Jour. Am. Med. Assn., 1911, lvi, 1457.

[12] In vital stained smears the platelets seemed slightly more plentiful than the counts indicated.

[13] Loc. cit.

April 15, and remained above 46,000 until April 30, when it was 16,000. During this period of higher counts there was essentially no bleeding. From May 2 to May 17 the count fluctuated between 10,000 and 50,000, during which time there was continued and increasing bleeding. There was no appreciable change in the count three days or five days after the sixth transfusion May 19, nor diminution in the bleeding. On May 24, the day following the seventh transfusion, the count was 60,000, the gums stopped bleeding, but the vaginal flow persisted. On May 27 the count was 3000. The only other counts in June were made on the 4th and 11th, when they were 20,000 and 6000 respectively. On August 14 the count was 12,000.

Duke[14] has shown that the life of the platelets is probably but a few days, and that the improvement after transfusion of cases with very few plates lasts for but a few days or until the platelets introduced have disappeared, unless the transfusion is successful in permitting the patient to supply or not destroy his own platelets and thus not return to his previous state of bleeding.

Such effect of transfusion on the platelets is seen in our patient after some transfusions, while after others the platelets increased very slightly or for a much shorter time. Perhaps this was because not enough blood was transfused or because there was something in the patient's blood that rapidly destroyed the foreign platelets. From the *in vitro* experiments described below this latter assumption would not seem true, but reactions *in vitro* are often not the same as *in vivo*. In a case reported by Drinker and Hurwitz[15] some transfusions were also not followed by a rise in the platelet count.

Le Sourd and Pagniez,[16] Ledingham and Bedson,[17] and Lee and Robertson[18] have shown that rabbits can be immunized against guinea-pig platelets; and that the serum from such rabbits (antiplatelet serum) will cause in dilutions as high as 1 to 328 macroscopic agglutination and lysis of normal platelets, while normal rabbit serum sometimes causes this only at times and in no greater dilution than 1 to 6. Animals inoculated with antiplatelet serum develop purpuric skin lesions, bleeding from the mucous membranes, a markedly diminished platelet count, and a delayed bleeding time. The coagulation time is but slightly altered and the clot does not retract. This condition resembles closely what is seen in cases of purpura hemorrhagica. The serum from animals injected with antiplatelet serum has no abnormal agglutinative or lytic action on the platelets *in vivo* or *vitro*.

In order to find out what effect our patient's serum had on platelets the following experiments were done. Washed and unwashed salt solution suspensions of platelets were obtained twice from a normal person and once from a case of purpura rheumatica with a platelet count of 290,000. Both of these individuals belonged to iso-agglutination group IV, to which our patient also belonged. To a series of tubes containing dilutions of from 1 to 3 to 1 to 120 of the serum from each of these individuals and the serum from our case there was added separately a few drops of each platelet suspension. In none of the tubes was there any macroscopic evidence of abnormal lysis or agglutination of the platelets. In the tubes with unwashed platelets clotting occurred in the lower dilutions, showing fibrinogen was present.

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[14] Jour. Exper. Med., 1911, xiv, 265.

[15] Arch. Int. Med., 1915, xv, 733.

[16] Jour. de physiol et de path. gén., 1911, xiii, 56.

[17] Lancet, 1915, i, 311.

[18] Lee and Robertson, Jour. Med. Res., 1916, xxxiii, 323.

Similarly suspensions of platelets were obtained from our patient when her platelet count was 60,000 and also from a normal person and added separately to the serum of both. There was the slightest suggestion that the patient's platelets after one hour were abnormally agglutinated by either serum.

Bleeding Time. Duke[19] observed that with a much reduced platelet count bleeding from a small puncture occurred for an abnormally long time. He blotted up on absorbent paper, at frequent intervals, the blood that flowed from a small puncture in the lobe of the ear. The duration of such a hemorrhage he called the bleeding time. The bleeding time of our patient from an ear prick of as near the same size as possible each time was determined by Duke's method, as often as the platelets were counted, sometimes more often. As has been noted by Duke,[20] [21] this time fluctuated with the number of platelets. A normal bleeding time of under three minutes occurred only when the count was above 60,000 excepting following the transfusion of March 24 when the count was 42,000. When the count was 1 to 5000 the bleeding time varied from a maximum of two to three hours even up to four hours March 10 (when a clamp was used to stop the bleeding) down to fifty to thirty minutes. When the count was 5 to 14,000, it varied from forty to twelve minutes. When 18 to 32,000, from eight to twenty minutes usually eight to twelve minutes, with the few counts between 46 to 60,000 about six minutes.

A difference of one or two minutes occurs in the normal bleeding time, and Duke[22] [23] has pointed out that no matter what the size of the puncture is this time will vary little. This seems to be true of normal cases; however, in this case where there was pathological bleeding time, I have noticed that the bleeding time was distinctly longer with a larger than a smaller puncture, a difference of thirty and fifty minutes frequently appeared.

Besides determining the bleeding time from the ear it was determined five times from a vein puncture in the forearm. Three times when the bleeding time from the ear was forty minutes to one and a half hours it was twenty to fifteen minutes from the arm and when two and a half minutes from the ear was thirty seconds from the arm.

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[19] Loc. cit. [20] Loc. cit. [21] Loc. cit. [22] Loc. cit. [23] Loc. cit.

Aynaud[24] found in normal animals about the same number of platelets in different arteries and veins. Nevertheless, it was thought that this difference of bleeding time from the capillaries of the ear and the vein of the arm might be due to a difference in the platelet count, but no special difference was found.

Attempts to Inoculate Animals. Besides the production of purpura hemorrhagica in animals by antiplatelet serum it has been produced by various poisons[25] that evidently act on the bone marrow as benzol, diphtheria toxin, tuberculin, etc.

Production of purpura by the injection of blood from patients into animals was accomplished in 1884 by Petrone[26] and in 1892 by Charrin.[27] However, they obtained positive cultures from the patients and animals of the same organism which was hemolytic in nature. Marchetti,[28] in 1910, also obtained from cases of purpura organisms that produced purpura in animals. Organisms of various sorts have been reported from cases exhibiting purpura, but there are many purpuric cases in which no organism has been found. Grenet[29] obtained purpura in rabbits by creating an hepatic lesion by temporary stasis of blood in this organ and injecting serum from purpuric and hemophilic patients into the spinal canal. His work was repeated with negative results by Crowell,[30] who also got no reduction of the platelet count by injections of benzol. Whether these various cases of purpura whose blood or the organisms from whose blood produced purpuric symptoms in animals had a much reduced platelet count, and therefore were cases of purpura hemorrhagica, is not known.

Injections of serum and blood from our patient into animals were unsuccessful in producing any purpuric manifestations.

Two rabbits of about 1200 gm. were each given intravenously for five days fresh serum collected within two hours previously. The first received three 2 c.c. injections and two 1.5 c.c. injections, and was found dead on the sixth day. Autopsy showed only an enlarged soft spleen and microscopically bacteria. Cultures were not made. The second rabbit received three 2 c.c. injections and two 1.6 c.c. injections, and remained well even after four months. Daily platelet counts, though fluctuating somewhat, were within normal limits in both animals. The white count in the second rabbit remained normal, as has been noted by Moss and Brown[31] after serum injections. The white count rose in the rabbit that died.

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[24] Arch. d. mal. du. cœur, 1911, iv, 358.

[25] Duke, Arch. Int. Med., 1913, xi, 100.

[26] Quoted in Nothnagel's System of Prac. Med., Am. ed., 1905, xi, 745.

[27] Compt. rend. Soc. de biol., 1902, liv, 427.

[28] Reviewed in Arch. d. mal. du cœur, 1911, iv, 466, from Congress de Méd. Int. Rome, December, 1910.

[29] Thèse de Paris, 1905, Jules Rousset, publisher.

[30] British Med. Jour., 1912, ii, 1102.

Loeb, Strickler, and Tuttle[32] have shown that about 6 to 10 c.c. of human serum per kilo of body weight rapidly kills when given intravenously. The serum from our patient was no more toxic for rabbits than normal serum, for 5 c.c. of normal human serum killed a 1100 gm. rabbit in six minutes and 4.5 c.c. of serum from our patient killed a 1120 gm. rabbit in one and a half hours.

With Dr. Sellard's help a monkey of about 3 kilos, while under ether, was given intrasplenically (after opening the peritoneum) by indirect transfusion about 13 c.c. of blood from our patient. This animal developed no abnormal symptoms after four months, and the formed blood elements and coagulating factors when examined after ten days were quite normal.

In view of the fact that blood cultures from the patient were negative, that the rabbit receiving serum from the same lot and in larger amounts than the rabbit that died remained well, and that the monkey did also, it is felt that death of the first rabbit from infection was due to faulty technic.

Were the case of purpura hemorrhagica similar to the purpura produced by antiplatelet serum in animals, the negative results obtained from injecting the patient's serum and blood into animals and from the tests for lysis of the platelets would be comparable to the negative results upon platelets obtained with serum of the purpuric animals *in vivo* and *in vitro*. This supposition may be true but has not been proved.

THE RETICULATED RED CELLS. The reticulated red blood cells (cells with a granulofilamentous substance stained by treating fresh blood with brilliant cresyl blue) were counted by the following method used by Hawes[33] and suggested by Wright.

A drop of freshly prepared solution of brilliant cresyl blue 1 to 1400 was dried on a microscope slide. Upon this dried stain was placed a drop of blood on a cover-glass. One thousand or two thousand red cells were counted in an area of the preparation, which was stained not too deeply or lightly, and the percentage of reticulated cells noted.

These cells are considered young cells. Their number and character give us a direct insight into the hemopoietic activity of the marrow. They normally comprise not over 1 per cent. of the red cells.

The reticulated cells in our case comprised on four different days between February 22 and March 6, 10 to 14 per cent. of the reds, which at this time averaged about 2,100,000. Before transfusion, March 11, they were 15 per cent., and the next day 10 per cent., rising to 19 per cent. March 15. Between March 17 and 24 they were 12 to 13 per cent., during which time the red count fell, reaching 920,000. Shortly after the transfusion on March 24, when the red count rose to 1,947,000, they were 8 per cent., rising to 15 per cent. March 27, when the red count had fallen to 1,043,000 and to 16 per cent. when the red count was 800,000. A similar though less marked fall and rise followed the transfusion of April 2. After this transfusion, when the red count was 2,320,000, the reticulated cells formed 5.25 per cent. of the reds. During the next eighteen days, as the red count rose, they formed about 7 per cent. of the reds. As the red count fell in early May the reticulated cells were usually about 10 per cent. They were then not counted until May 29, when after the transfusion on this day they were 9 per cent. and on June 15, 12 per cent., and August 14, 7 per cent.

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[31] Johns Hopkins Hosp. Bull., 1911, xxii, 258.

[32] Virchows Archiv., 1910, cci, 5.

[33] Boston Med. and Surg. Jour., 1909, clxi, 493.

These cells were always present in abnormally high numbers, higher when the red count was lower, a time when one would expect a greater effort on the part of the marrow to regenerate blood cells. Shortly following transfusion there was a drop, followed a few days later by a rise which would be expected if the transfused blood acted to stimulate the marrow. Vogel and McCurdy[34] have observed this effect of transfusion on the reticulated cells in cases of pernicious anemia.

Reports on the condition of the marrow in cases of purpura hemorrhagica with low platelet counts are rare. Hyperplastic myeloid and aplastic marrow are reported. It seems that cases presenting the symptoms of purpura hemorrhagica due to aplasia of the marrow (as evidenced by a leukopenia, lymphocytosis, and diminished or absent reticulated cells) are more properly cases of aplastic anemia, and that purpura hemorrhagica not complicating other diseases and without known etiology but without evidence of aplastic marrow belongs to another group.

Vogel and McCurdy[35] cite a case of purpura hemorrhagica that had no reticulated cells, a marked leukopenia, and that did not respond to transfusion. Though the bleeding in this case was evidently similar to ours, the percentage of the reticulated cells and the white count were the opposite. Their case perhaps would be more properly called one of aplastic anemia, with symptomatic purpura hemorrhagica.

Vasquez[36] pointed out that the disappearance of reticulated red cells in pernicious anemia is a strong argument for the diagnosis of aplastic changes in the marrow. That a marked reduction or absence of these cells speaks for an aplastic marrow has been also emphasized by Pepper and Peet[37] and Musser.[38]

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[34] Arch. Int. Med., 1913, xii, 707.

[35] Loc cit.

[36] Bull. et mém. Soc. méd. d'hôp. de Paris, 1907, xxiv, 1532.

[37] Arch. Int. Med., 1914, xii, 81.

[38] Ibid.,xiv, 275.

The reticulated cells were diminished in two cases with aplastic marrow that I have studied. One, a case of aplastic anemia proved at autopsy, showed no reticulated cells in several smears. The other, the case mentioned before of poisoning with benzol (a substance that produces aplasia of the marrow) showed at first an exceedingly rare reticulated cell, but after the fifth transfusion when the case improved, the reticulated cells were 3 per cent.

Vogel and McCurdy[39] consider that the total absence of reticulated cells in their case showed complete inability of the marrow to respond to stimulation by transfusion, which with the low white count would most certainly suggest an aplastic marrow. That cases with aplastic marrow have a very low percentage of reticulated cells seems certain. Such cases may have purpura hemorrhagica due to the aplasia. Our case does not fall into this group on account of the constant high percentage of reticulated cells, no leukopenia, often a leukocytosis, and no marked lymphocytosis.

The reason for the very low platelet count in our case might perhaps have been due to some localized aplastic condition of the platelet forming elements, which in turn might have been due to some specific poison. It seems very unlikely that there was any aplasia of the elements that form the red or white cells. If there was no localized aplasia it seems that the low platelet count was due to some specific reaction (presumably a specific poison) that destroyed the platelets as fast as they were formed. Possibly there was a combination of a localized aplasia and a destruction of formed platelets as the cause for the low platelet count.

Coagulation of the Blood. Normal, decreased, and increased coagulation time of the whole blood are reported in cases of purpura. Such conflicting reports are probably due to different technics and different types of purpura at different stages of the disease.

In the cases with low platelet counts, Duke[40] has found a normal coagulation time. Other observers give increased or normal coagulation time for these cases.

There have been few determinations of prothrombin and antithrombin in such cases.

Austin and Pepper[41] and Whipple[42] found an antithrombin increase. Minot, Denny and Davis[43] found the antithrombin normal or slightly above or below normal. Howell[44] found no abnormality.

In experimental benzol poisoning with reduced platelet counts, Hurwitz and Drinker[45] have shown that there is a lessened amount of prothrombin which does not always vary directly with the number of platelets. The antithrombin was normal.

The oxalated plasma from Lee and Robertson's purpuric animals

[39] Loc. cit.

[40] Loc. cit.

[41] Arch. Int. Med., 1913, xii, 637.

[42] Ibid., xi, 305.

[43] Loc. cit.

[44] Ibid., 1914, xiii, 76.

[45] Jour. Exper. Med., 1915, xxi, 401.

which I examined showed a slightly delayed prothrombin time with normal antithrombin.

Minot, Denny and Davis[46] noted that cases with low platelet counts may or may not have a delayed coagulation time, and that with the delayed coagulation time there was a delayed prothrombin time. They felt that perhaps cases with excessively few plates always had a somewhat delayed coagulation time.

Determinations of the coagulation time, prothrombin and antithrombin were made in our case and the results given in Table I.

The coagulation time was determined by the method described by Lee and White,[47] normal being five to nine minutes. With the low platelet counts the clots were non-retractile and weak. The clot on April 15, when the platelet count was higher, retracted very slightly.

The prothrombin and antithrombin were determined by Howell's method as discussed by Minot, Denny and Davis.[48] The test for prothrombin is one for its relative efficiency, and consists of determining the time (prothrombin time) that it takes an oxalated plasma to clot on recalcification with the optimum amount of calcium; that is, the amount that causes the most rapid clotting.

As the table shows, the blood of our case had a delayed coagulation time associated with a delayed prothrombin time, with one exception when both were normal. These times, though usually but slightly abnormal, were once quite markedly so. They did not vary directly with the platelet count or clinical symptoms. The antithrombin was normal. The fibrinogen was not determined accurately, but was probably not markedly diminished, as was told by the amount of precipitate formed on heating the plasma to 60° C.

TABLE I.

Date.	Coagulation time (minutes), case.	Coagulation time (minutes), control.	Prothrombin time (minutes), case.	Prothrombin time (minutes), control.	Antithrombin factor.	Platelet count.	Clinical condition.
Feb. 17 A.M. . .	23	8½	30	12	1.2	1,200	Very marked bleeding.
Feb. 17 P.M. . .	27	8	26	12	. .	. .	Very marked bleeding.
Feb. 20 . .	20	8	20	12	1.2	10,000	Marked bleeding.
Feb. 22 . .	11	9	15	11	0.8	22,000	Very little bleeding.
Feb. 23 . .	11½	9	16	13	1.0	. .	Very little bleeding.
Feb. 25 . .	20	8	20	12	. .	26,000	Very little bleeding.
Mar. 1 . .	18	9	25	14	. .	5,000	Marked bleeding.
Mar. 6 . .	10	7	15	12	1.1	1,600	Very marked bleeding.
April 15 . .	6	8	8	8	0.87	75,000	No bleeding.

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[46] Loc. cit.

[47] Am. Jour. Med. Sc., 1913, cxlv, 495.

[48] Loc. cit.

Other studies were made on the coagulation of the blood, some of which are as follows. The first was done by Dr. Lee.

1. Washed and unwashed platelets were found to have fully as much thromboplastic activity as normal platelets. This agrees with Fonio's[49] hypothesis that though the plates are lacking in numbers in this disease, they are not lacking in activity.

2. Salt and water extracts of the uterus accelerated the clotting of normal oxalated plasma. There was thus no evidence of deficient thromboplastic activity as a cause for bleeding.

3. The syphilis coagulation test as described by Hirshfeld and Klinger[50] and also Fränkel and Thiele,[51] which gives a marked delay in syphilis, was done twice. Both times there was a slight delay, but no such marked delay, as is seen with syphilis.

4. Howell[52] has recently studied the clotting of blood under the ultramicroscope and has found different appearances of the fibrin needles under different conditions. He suggested that perhaps one might detect abnormalities of the blood in disease by this method. Dr. Howell very kindly studied the clotting with thrombin of a specimen of oxalated plasma from our case, but was unable to detect any abnormality. On another specimen I likewise found by this method the clotting to appear normal.

THE TOURNIQUET SIGN. The effect of placing a tourniquet about the arm for three minutes so that the return blood flow is shut off was studied. This test is considered a test for the manifestation of diminished resistance in the walls of the smaller blood-vessels. Frugoni and Guigni[53] believed that this test was positive in cases with a tendency to hemorrhagic manifestations.

Morandi[54] has studied the test and has found it positive in a wide variety of diseases. Hess[55] has found it positive in cases of scurvy. In describing the test, Hess states that "after the pressure is removed and the arm loses its cyanosis one looks for petechiæ below the point of constriction, but no importance should be attached to minute petechiæ that appear just below the pressure band as these are often found in normal cases." In our case the test was done with these precautions.

On February 16, when there were many purpuric spots on the skin, this test was strikingly positive, spots even as large as a ten-cent piece appearing rapidly in the skin below the tourniquet. On the following days, as the lesions all over the skin faded, the test became practically negative, reappearing with the recurrence of fresh spots on the body.

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[49] Mitt. a. d. Grenzeb. d. Med. u. Chir., 1914, xxviii, 313.

[50] Deutsch. med. Wchnschr., 1914, xl, 1607.

[51] München. med. Wchnschr., 1914, lxi, 2095.

[52] Amer. Jour. Physiol., 1914, xxxv, 143.

[53] Semaine méd., 1911, xxxi, 25.

[54] Summary, Jour. Am. Med. Assn., 1912, lix, 1555.

[55] Am. Jour. Dis. Child., 1914, viii, 386.

Following the transfusion, March 8, the patient developed no skin lesions until May 11, a time when she had gone the longest during her hospital career without a transfusion. From March 8 to May 11 there appeared rarely a few minute spots on the arm below the tourniquet (no tests between April 25 and May 10), and during the following week, when purpuric skin lesions reappeared, the tourniquet sign was positive, though not as striking as in February. After the transfusion May 18 and until the patient left the hospital July 4 there were no noteworthy skin lesions, seldom a positive tourniquet sign, and then of slight degree. However, on August 14, when the patient had had no transfusion for even a longer period than when in the hospital, and there were purpuric spots scattered on the arms and legs, the sign was present but not striking. Thus the most positive tourniquet sign occurred when there were spontaneous purpuric spots on the skin. Whether the transfusions had any effect in preventing recurrence of skin lesions cannot be told until other cases are studied.

MISCELLANEOUS STUDIES. 1. Both Goodpasture[56] and the work of Gley and Le Bas[57] suggested that there might be a fibrinolytic ferment in the blood of purpura hemorrhagica cases. Goodpasture[58] has shown that such a ferment exists in the blood of cases of atrophic cirrhosis. However, no fibrinolytic ferment was found in our case.

2. Robertson determined by Wilbur and Addis's[59] method the urobilin content of the stools during the week of April 15. He found no abnormality, thus indicating there was no increased blood destruction.

3. On several occasions the hydrogen ion concentration of the blood was determined by the method described by Levy, Rowntree and Marriott[60] and by a slight modification of this method. In all instances the concentration was normal.

4. The fragility of the washed red corpuscles was tested by means of various strengths of salt solution. Both the patient's and normal red cells began to hemolyze in 0.45 per cent. salt solution. The patient's cells were completely hemolyzed in 0.26 per cent., and the controls in 0.30 per cent.

SUMMARY AND CONCLUSIONS. A case of idiopathic purpura hemorrhagica, occurring in a girl of eighteen is presented. The case had an abnormally low platelet count which is typical of this condition. The low platelet count seemed to have been due to one or both of the following two factors:

1. Some reaction (presumably a specific poison) taking place in the body which destroyed the platelets as fast as they were formed.
2. A localized aplasia of the platelet-forming elements of the marrow which might have been due to some toxic phenomena.

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[56] Personal Communication.

[57] Arch. de physiol. norm. et path., 1897, ix, 848.

[58] Johns Hopkins Hosp. Bull., 1914, xxv, 330.

[59] Arch. Int. Med., 1914, xiii, 235.

[60] Ibid., 1915, xvi, 389.

This destructive process, perhaps toxic, anaphylactic, or of some other nature, seems to have been specific because none of the other formed blood elements were involved.

The anemia was easily explained by hemorrhage. There was no evidence of red cell destruction as shown by the urobilin tests. The white cells were not affected.

The case was not one of aplastic anemia, *i. e.*, with generalized aplasia of the marrow, because there was no leukopenia, no marked lymphocytosis, and there was always a high percentage of reticulated red cells. In cases with aplasia of the bone marrow these cells are absent or very rare, and when increased probably signify activity of the red cell elements of the marrow.

The specificity of this reaction on the platelets simulates in every way animals injected with antiplatelet serum.

In vitro the patient's serum caused no abnormal lysis or agglutination of normal platelets.

Injections of patient's serum and blood into animals were negative.

There was usually a delayed coagulation time, a weak, nonretractile clot associated with a delayed prothrombin time which did not vary directly with the platelet count or clinical symptoms. The antithrombin was normal. The platelets were actively thromboplastic as were extracts from the uterus. Very slight delay of coagulation occurred with the syphilis coagulation test. The clotting of the plasma with thrombin as seen under the ultramicroscope was normal.

The tourniquet sign was greatest when there were spontaneous purpuric lesions on the skin.

The bleeding time varied with the platelet count becoming longer as the platelets diminished.

The bleeding time was longer with a larger than a smaller puncture.

The bleeding time from the arm vein was shorter than from the ear, which was not due to a difference in the platelet count.

The essential treatment consisted of trying to replace the lacking platelets by eleven transfusions of normal blood and by giving locally and subcutaneously thromboplastic substances which contain one of the active principles of platelets.

Transfusion resulted in, usually but not always, temporary improvement of the patient's condition, in turn associated with a temporary rise of the platelet count.

Thromboplastic substances were perhaps of benefit in temporarily controlling hemorrhage.

In spite of the persistent therapeutic procedures the course of the disease was very little affected, and the patient died thirteen months after the onset of her illness.

THE SPINAL-FLUID SYNDROMES OF NONNE AND FROIN AND THEIR DIAGNOSTIC SIGNIFICANCE.

By Frederic M. Hanes, M.A., M.D.,
PROFESSOR OF THERAPEUTICS, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VA.

G. Froin[1] reported in 1903 three cases which upon lumbar puncture showed spinal fluids yellow in color (xanthochromia), containing numerous cells, and which, upon standing, coagulated spontaneously and massively, owing to their high fibrin content. The phenomena thus described were new to medical literature, and they have since been collectively designated "Froin's syndrome." Later observers, using more accurate methods of cell enumeration, have not confirmed Froin's finding of "numerous cells," and pleocytosis cannot be regarded an essential part of the syndrome. This point will be discussed later.

Some five years after Froin's publication, M. Nonne[2] reported three cases of cord tumor, the spinal fluids of which contained an excess of proteid (strongly positive phase I) with no leukocytosis (pleocytosis) of the fluids. Nonne was unable to interpret the dissociation of proteid excess and pleocytosis in his three cases, and did not feel from his limited experience that any positive diagnostic significance could be attributed to the syndrome in relation to spinal-cord tumors.

Since the appearance of these two contributions the literature has been augmented by several papers dealing with either one or the other of these two syndromes, but no one has suggested that they are closely related phenomena. In this communication we shall bring forward evidence, both from our own experience and the literature, with the object of proving that the syndrome of Nonne is simply the early manifestation of a process which in its later and terminal phases gives rise to the syndrome of Froin. We shall try, furthermore, to show that the Nonne-Froin syndrome when properly interpreted is of the greatest practical assistance in the differential diagnosis of spinal-cord lesions.

Xanthochromia, or yellow pigmentation of the spinal fluid, has been described by many observers, and cannot be regarded as a rarity. We have seen five instances of this condition in the past three years. It is such a striking and unexpected finding at lumbar puncture that it has assumed a larger share of importance than it deserves. It will be necessary to define clearly the exact condition which can properly be termed xanthochromia, for hemorrhage into the cerebrospinal fluid from ventricular apoplexy, traumatic rupture of meningeal vessels, or other causes leads to a condition which has been designated erythrochromia, and this hemorrhagic pigmentation has been frequently confused with xanthochromia. The two conditions possess certain characteristics which permit of their ready differentiation.

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[1] Gaz. d. hôp., 1903, 000, 000.

[2] Quoted by Raven, Deutsch. Ztschr. f. Nervenk., 1914, xliv, 380.

1. The color in erythrochromia varies from a bright red through varying shades of reddish-brown, reddish-yellow to a dark yellow color. Lumbar punctures made at intervals of several days on a case with hemorrhagic spinal fluid have shown a variety of color changes (Schwarz), whereas the color in xanthochromatic fluids remains the same from puncture to puncture. The shades in xanthochromia are described as amber, cream, or straw colored, and instances are recorded in which the color remained the same throughout several months.

2. In erythrochromatic fluids red blood cells or their shadows may be very numerous. In a case which we saw recently, in which the patient had fallen upon his head from a swiftly moving automobile, the spinal fluid was the color of arterial blood and red blood cells were present in very large amount. From this extreme picture lesser grades of erythrocytosis are found, and finally only shadows of red cells or a reddish-yellow pigmentation remains as evidence of former hemorrhage. Such fluids, however, yield positive chemical test for blood, although in later stages the spectroscope may fail utterly to reveal characteristic bands. Furthermore, owing to the meningeal irritation of the products of red-cell destruction, a leukocytosis of the fluid develops. Schwarz reports such a case in which there were numerous shadows of red cells and 268 white cells (mostly lymphocytes) to the cubic millimeter of fluid. In xanthochromia the white cells are, as a rule, not increased; there are no red cells, and the fluid does not yield either chemical or spectroscopic evidence of hemoglobin derivatives. When the white cells are increased it is evidence of meningeal inflammation.

3. The fibrin content of xanthochromatic fluids is extremely high. The citron-yellow fluid, which is quite limpid, coagulates spontaneously, and in so massive a manner that the containing test tube can be inverted without loss of its contents. The coagulum is gray or white. This is not true of erythrochromatic fluids. They may contain fibrin to a certain extent, but they do not coagulate massively.

4. Both xanthochromatic and erythrochromatic spinal fluids contain proteid substances in very large amount, but whereas in xanthochromia a large excess of proteid is a constant and characteristic part of the picture, in erythrochromia the proteid tends to decrease in amount the further away in time from the hemorrhage the fluid is removed.

In purulent meningitis the spinal fluid may be colored yellow, brown, or green, but there is no danger whatsoever of confusing such a finding with any other, owing to the presence of pus cells in enormous amounts and of bacteria.

The syndrome of xanthochromia with massive coagulation of the spinal fluid and high proteid content, with or without pleocytosis, is always produced by a localized obliteration of the pia-arachnoid space which divides it into two parts, an upper one in free communication with the pia-arachnoid spaces of the upper cord and brain and a lower cul-de-sac. In this lower cul-de-sac the fluid gradually changes in character from the normal limpid spinal fluid to the xanthochromatic type of fluid just described. The following briefly summarized case will illustrate perfectly the conditions leading to the xanthochromia-syndrome:

A child of nine months was admitted to the hospital suffering from spastic paralysis of both arms and legs. Upon the least stimulus the arms, legs, and trunk would pass into a tetanic spasm. Lumbar puncture revealed a fluid the color of picric acid, containing sixteen cells to the cubic millimeter, a very great excess of proteid, and the fluid coagulated massively on standing. After a few days it was observed that the child's fontanelles were bulging markedly, and to relieve the tension a needle was inserted through the anterior fontanelle and 30 cm. of perfectly normal limpid cerebrospinal fluid was withdrawn. This fluid contrasted strongly in every way with that removed by lumbar puncture.

The child died, and at autopsy a large mass of tuberculous granulation tissue was found completely encircling the medulla and quite obliterating the pia-arachnoid space at the level of the foramen magnum. The mass of new growth had completely separated the pia-arachnoid spaces of the cord from those of the brain.

Another instance of the syndrome under discussion was seen recently in a man, aged twenty-seven years, who for a year had suffered from a painlessly developing paraplegia which had terminated in an utter spastic paralysis of both legs. The history and physical findings indicated cord compression at the level of the seventh dorsal segment, and at operation a cyst of the pia-arachnoid was discovered which was completely obliterating the pia-arachnoid space and compressing the spinal cord. Below the site of this compression the veins of the pia were much engorged and tortuous. The cyst was drained, and six weeks after operation a lumbar puncture revealed a fluid normal in every respect. The paraplegia improved remarkably following operation.

Three other instances of the xanthochromia syndrome which we have studied were in cases of extramedullary spinal-cord tumors, situated at various levels of the cord. In every instance, however there was produced by the tumor a cul-de-sac below the site of cord compression, and following the removal of the tumor the spinal fluid regained its normal characteristics.

The literature of xanthochromia with massive coagulation has been reviewed recently by Mix.[3] He says: "Whenever the spinal fluid is found to conform to this syndrome it means that there is an isolated cul-de-sac. It may be isolated by meningitis, which has sealed the meninges to the surface of the cord, or it may be due to a pachymeningomyelitis or to a tumor which compresses intradurally, and so "cuts off by pressure the cul-de-sac, or to an intradural tumor which acts as a ball-valve, plugging up the top of the lumbar enlargement of the spinal cavity." With this statement our own experience is in complete agreement, and from this clear description of the mechanism of production of the syndrome the great practical diagnostic importance of the finding will readily be appreciated. Any pathological alteration of the vertebræ, dura mater, or pia-arachnoid which leads to partial or complete obliteration of the pia-arachnoid space and the formation of a cul-de-sac is capable of producing the syndrome of xanthochromia with excess proteid and massive coagulation. If the pathological change is associated with inflammation of the meninges there will be a leukocytosis of the fluid, but when the compression is due to non-inflammatory growths it is our experience that no pleocytosis is present. When cellular elements are present in more than normal amount, syphilis or tuberculosis should be strongly suspected.

The origin of the pigment in xanthochromatic fluids has led to some discussion. It has been suggested that the color in the last analysis is due to blood pigment from multiple small hemorrhages (Schwarz,[4] Kafka,[5] Raven[6]). We believe from our observations that the xanthochromia syndrome is produced by transudation of blood serum into the pia-arachnoid cul-de-sac, owing to stasis produced by pressure upon the veins of the pia at the site of cord compression. The high content of such fluids in fibrin and proteids, and the presence in them of few cells, supports the view that we are dealing in these cases with a transudate which is perfectly analogous to pleural transudates due to venous compression. One has only to recall the circulatory conditions in the spinal cord to realize how pressure upon the venous return flow would naturally lead to stasis with transudation. Multiple small hemorrhages, on the other hand, would produce the condition of erythrochromia, which, as we have pointed out, possesses characteristics which distinguish it from the xanthochromia syndrome.

At the beginning of this paper we stated that the findings of Nonne—namely, high proteid content with no pleocytosis—in three cases of cord tumor were closely related to Froin's syndrome of xanthochromia, with massive coagulation. It remains to make clear this connection.

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[3] Murphy's Clinics, 1915, iv, 187 (full literature).

[4] Deutsch. Ztschr. f. Chir., 1913, cxxiv, 346.

[5] Ztschr. f. d. ges. Neurol. u. Psychiat., 1912.

[6] Loc. cit.

Raven,[7] a pupil of Nonne, has contributed a very valuable paper from Nonne's clinic reviewing 47 cases of cord tumor—20 from the experience of the clinic and 27 from the literature—in which the proteid content (phase I) of the spinal fluids was high with low cell count (no pleocytosis). His article is deficient in that he does not state how many of these cases showed xanthochromia and massive coagulation. That some of his cases did show these phenomena is obvious from his discussion and conclusions. In his series the findings ranged from slight proteid increase without coloration of the fluid to frank outspoken xanthochromia with great excess of proteid and massive coagulation. Although he clearly recognizes that cord compression is the cause of the proteid increase, xanthochromia, etc., he fails to make clear the all-important fact that xanthochromia with massive coagulation is but the terminal picture of a process which begins with an increase of proteid without pleocytosis as its sole distinguishing feature. In a series of spinal fluids from cord-compression cases every gradation can be traced from proteid excess alone to marked xanthochromia with an enormous excess of proteid and massive coagulation.

Mestrezat in his monograph on the cerebrospinal fluid (Paris, 1912) reports nine cases which illustrate the early stages of the Nonne-Froin syndrome. He speaks of them as "les cas frustes," or imperfectly developed examples of the xanthochromia—syndrome. Some of these cases failed to show xanthochromia; others showed no pleocytosis, though yellow in color and coagulating spontaneously; still others exhibited variations in the formation of a coagulum. As one reads these cases in the light of what has been said previously in this paper, one has no hesitancy in classing them among the type of cases reported by Nonne; they represent stages more or less advanced in the Nonne-Froin syndrome.

Under the title "Dissociation albumino-cytologique an cours des compressions rachidiennes," Sicard and Foix[8] have published interesting observations upon the spinal fluids of patients suffering from active Pott's disease. They found the albumin content of such fluids abnormally high, but with no accompanying pleocytosis, and, as indicated in their title, they attribute their findings to cord compression by the tuberculous vertebræ. They likewise mention that twelve cases of cord tumor showed increase of albumin with no plecytosis. It is thus evident that compression of the cord from whatsoever cause leads to an excess of proteid in the spinal fluid, and that when the meninges are not involved, there is no abnormality in the cell count.

We are convinced that the prominence which Froin's syndrome of xanthochromia with massive coagulation has assumed in the literature is due to the fact that the striking yellow color and spontaneous coagulation of the fluid cannot possibly be overlooked, whereas proteid increase alone requires laboratory experience for its demonstration and interpretation. It is perfectly obvious though that if evidence of cord compression is to be obtained from the spinal fluid, it is important to elicit this evidence before the terminal phase of xanthochromia with massive coagulation is established. Proteid increase without pleocytosis has the same significance in the early stage of cord compression that the full-blown xanthochromia syndrome has in the later stage of more or less complete paraplegia. Indeed, the stage of xanthochromia with massive coagulation may never be reached, and only the early phase of proteid excess without pleocytosis exist as evidence of cord compression.

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[7] Loc. cit.

[8] Sicard and Foix, Presse méd., 1914, xx, 1013.

CONCLUSIONS. 1. Compression of the spinal cord and its meninges from whatsoever cause leads to the formation of a cul-de-sac, more or less complete, distal to the site of compression. This leads to characteristic changes in the spinal fluid.

2. The earliest characteristic change has been described by Nonne as an increase of proteid (phase I positive) without cell increase (pleocytosis).

3. As the condition of cord compression persists, the fluid gradually becomes yellow in color (xanthochromia), the proteid content increases enormously, and the fluid, when removed, coagulates spontaneously (Froin's syndrome). Pleocytosis may or may not be present, depending upon whether or not the meninges are inflamed by the pathological process causing the compression.

4. Xanthochromia of the spinal fluid must be distinguished from staining of the fluid by hemoglobin derivatives (erythrochromia).

5. The spinal-fluid syndrome of Nonne-Froin is very helpful and reliable in the diagnosis of spinal-cord lesions. When present it always indicates a compressive lesion of the cord.

CHYLOTHORAX. REPORT OF A CASE.

By Philip Lewin, M.D.,

CHICAGO.

INTRODUCTION. Chylothorax is a condition in which the pleural cavity contains chyle. This condition may be due to a rupture of the thoracic duct or its radicles, or to some pathological condition of their walls, whereby the contents may be transuded into the pleural cavity. Chyle is lymph derived from the walls of the alimentary tract.

INFREQUENCY. Handmann, writing in 1899, in reviewing the literature of 261 years, was able to collect only 41 cases of chylothorax.

Baldwin, in 1908, brought the number up to 47 cases of genuine chylothorax and 15 doubtful cases. In 1912 Sale added 1 case. In 1913 De Lange and Grunder each reported 1 case, and with the present case the total number to date is, so far as I am able to find, 51 cases in two hundred and seventy-seven years of medical literature.

There is no doubt that many more cases have occurred: some never having been diagnosed; others diagnosed but never reported. These cases have been overlooked because the condition can be diagnosed only by the exploring needle or postmortem examination.

The diagnosis depends upon four factors:

1. Physical examination.
2. Roentgen-ray examination to demonstrate fluid in the chest.
3. History of
    - Trauma;
    - New growth or
    - Liability to obstruction.
4. Aspiration and examination of fluid.
    - Chemically,
    - Microscopically, and
    - Biologically.

The case I wish to report is that of H. A., male, born in Sweden, aged fifty years. He entered St. Luke's Hospital April 3, 1914, on the service of Dr. R. B. Preble, having been referred by Dr. Gilbert, of Chicago Heights.

History as obtained by Dr. Cameron is as follows:

Complaint. Large abdomen.

Family History. Mother died of tumor of pelvis; nature unknown.

Past History. General health has been good. Formerly troubled with headaches and occasionally a dizzy spell on change of position. No symptoms of tuberculosis. Appetite always good. No distress after meals. No vomiting or hematemesis. No jaundice or colic. Denies venereal infection, and careful questioning does not reveal any evidence of same.

Habits. Good.

Weight. Getting poorer in flesh, but gaining in weight, since abdomen began to increase in size.

Present Trouble. One year ago patient first noticed that his abdomen was increasing in size. No pain, vomiting, or distress after eating. Appetite good. Slight dyspnea but no edema of ankles. No jaundice or colic. Abdomen continually increasing in size symmetrically.

Four months ago patient first noticed a few small subcutaneous lumps over chest wall and abdomen. Few inguinal glands, which had always been palpable, were increasing in size. Axillary glands were growing larger and were easily palpable. No pain or inflammation.

Four weeks ago patient noticed that the scrotum and prepuce were swelling, the latter causing difficulty in micturition.

One week ago edema of ankles appeared. Patient had four or five bowel movements daily, which were black in color and fairly well formed. He never noticed any blood in the stool.

Physical examination made by Dr. C. P. Clark and the writer April 5, 1914:

General Considerations. Patient is a white male, aged fifty years, six feet tall, and 175 pounds in weight. Well developed, but state of nutrition poor at present. Circumference of chest, 36 inches; of abdomen at umbilicus, 40 inches. No marked dyspnea in the recumbent position. No apparent pain. He is able to be up and about. Skin is dry and loose except over abdomen, where it is very tense and shiny. Hair is scant and dry. No seborrhea. Acne present. No scars of any kind. No tenderness over long bones or sternum. No evidence of present or former fractures. There is an exostosis of the right ilium. The umbilicus is prominent, but there is no hernia. So far as can be determined under the abnormal condition of the scrotum there is no evidence of inguinal hernia. No femoral hernia. No evidence of present or former inguinal abscess.

Nervous System. Mental condition normal. No anesthesias or paresthesias. Knee-jerks very sluggist. Plantar, abdominal, and corneal reflexes absent; faucial reflex practically gone. Arm and jaw reflexes active. There is a coarse tremor of the lips, tongue, and fingers, but none of the head. Babinski, Oppenheim, and Gordon signs negative, also Kernig and Romberg. No ankle clonus. Pupils equal and react to light and accommodation. No strabismus or nystagmus.

Ears. Air conduction on left side very poor. Bone conduction poor on both sides.

Circulatory System. Blood-pressure: systolic, 138; diastolic, 92; pulse-pressure, 46. Moderate sclerosis of all superficial arteries. Veins all over the body are prominent, especially those of the thorax and epigastrium. No caput medusæ. No clubbing of fingers. Capillary pulse is present. Radial pulse is eighty per minute, regular, full, and moderately hard.

Heart: No bulging at base or apex. Small area of pulsation in suprasternal notch, also in the supraclavicular fossæ. No thrills. Auscultation reveals normal heart tones throughout. No evidence of aortic aneurysm. When the patient is in a recumbent position with arms thrown above his head there is a very marked tumor-like distention of the jugular vein above on each side; also of the superficial cervical veins. This dilatation disappears when he sits or stands.

Respiratory System. Septal spur. Throat hyperemic. Some depression of supra- and infraclavicular fossæ with atrophy of supra- and infraspinati muscles. Intercostal spaces are depressed. Ribs are prominent. Chest symmetrical. Thoracic respiration defective. Vocal fremitus increased over right chest, superiorly especially. (For results of percussion see Figs. I to IV.)

Auscultation: Breath sounds distant over areas of dulness. Few crackling rales heard at the end of inspiration over the right infra-axillary space. No bronchial breathing heard over any part of the lungs. There has been no cough or expectoration during this examination.

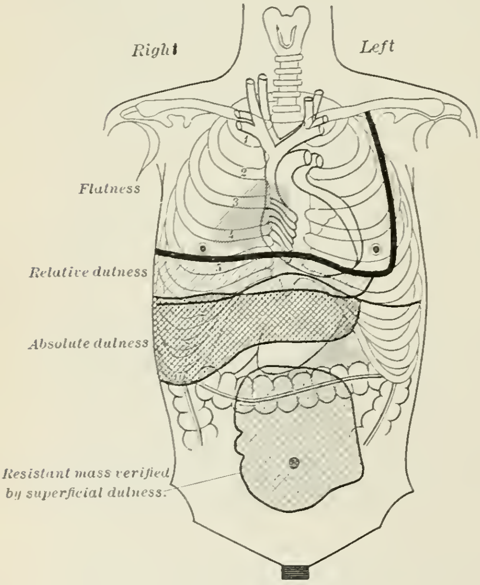

FIG. I.—Patient lying.

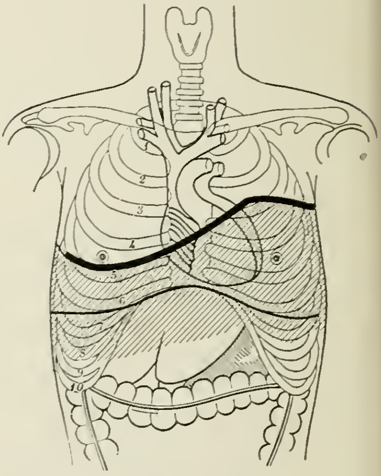

FIG. II.—Patient sitting.

Digestive System. Lips and tongue normal. Breath offensive. Gingivitis and pyorrhea present. Abdomen very prominent and symmetrical. No bulging in flanks. Umbilicus very prominent. Abdominal wall edematous. Palpation reveals a tense abdomen with a dense palpable mass of the size and shape as noted in Fig. I. This mass appears to be solid. Margins are more or less irregular. It is movable and slightly tender. Liver and spleen cannot be outlined definitely by palpation. There is a tympanitic area surrounding the tumor and the lumbar regions show dulness.

Genito-urinary System. Kidneys not palpable because of tenderness of abdomen. Bladder not distended. Penis and scrotum markedly edematous. Prepuce edematous and cannot be retracted. Testes normal. No varicocele. Vasa not palpable.

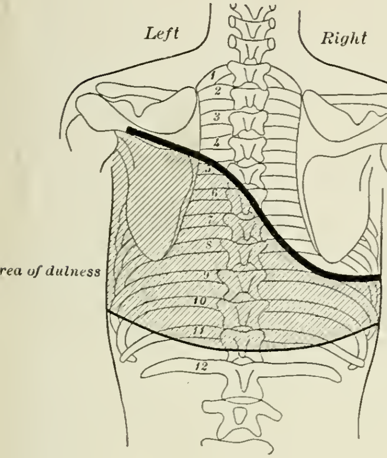

FIG.—III.—Patient sitting.

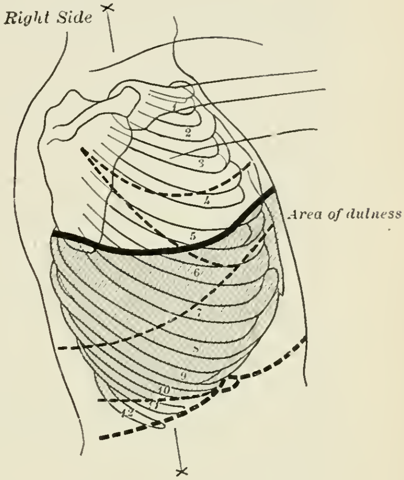

FIG. IV.

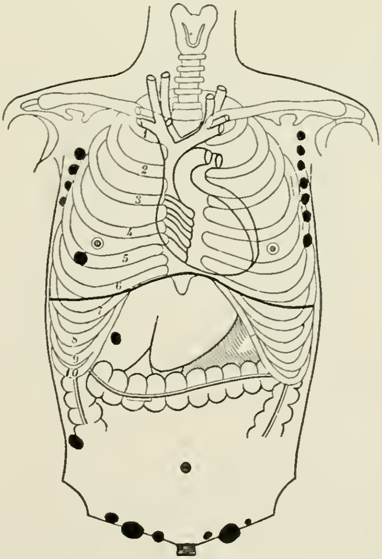

FIG. V.

Glandular System. Thyroid atrophied. Thymus not in evidence. (See Fig. V, showing enlarged lymph glands.) Epitrochlear glands each the size of a small bean. Axillary glands enlarged.

Cervical glands shotty. Salivary glands normal. The inguinal glands on both sides are greatly enlarged, there being one on the right side about the size of an English walnut and one on the left side as large as a small hen's egg. There is a chain of glands in the axilla on each side, each about the size of a filbert. There is one small gland in the region of the right nipple, one in the right lumbar region, one in the left lower quadrant, and one below the right costal margin. Femoral glands are also enlarged. Popliteal glands cannot be palpated.

Rectal Examination. No hemorrhoids. No impaction of feces. Sphincter has good tone. Prostate normal. Vault of rectum is tense and bulging. There is possibly palpable a lobulated mass.

Urinalysis: Albumin positive; sugar negative; no casts; no chyle.

Blood. Red-blood cells, 4,600,000; white-blood cells, 18,760. Hemoglobin, 85 per cent.; color index, 92. Lymphocytes: small, 55 per cent.; large, 7.5 per cent.; indentate nucleus, 1 per cent.; neutrophilic myelocytes, 1 per cent.; polymorphonuclear neutrophiles, 33 per cent.; eosinophiles, 0.5 per cent.; basophiles, 1 per cent.; unclassified, 1 per cent. In stained specimen reds seem normal.

Roentgen-ray examination by Drs. Case and Van Horn on April 6, 1914, revealed "Hydrothorax involving the right half of the chest. Level of fluid (patient standing) about the sixth rib posteriorly."

On April 8 and 21 punctures of the pleura were made and 48 and 54 ounces of fluid respectively were removed.

Dr. Moody's report on fluid: Opaque, milky, red; no odor; sp. gr., 1017. Alkaline; albumin positive; sugar negative. Urea, 0.6 per cent. Many red-blood cells. Large amount of fat.

Dr. A. J. Carlson, department of physiology, University of Chicago, reports that fluid is true chyle with the admixture of a small amount of blood.

On April 14, 1914, a gland was removed from below the right costal margin by the writer. Examination by Drs. Le Count and Moody revealed a diagnosis of small round-cell sarcoma? Lymphosarcoma or pseudoleukemia.

On April 18, 1914, a gland removed from the inguinal region by Drs. L. L. McArthur and T. J. Gunther. Diagnosis: round-cell sarcoma.

Subsequent History. On May 12, 1914, the patient left the hospital and returned to Chicago Heights, where he died September 24, 1914. Paracentesis of the chest was performed about once every two or three weeks and about 1 liter of fluid removed several times, then the amount removed was gradually decreased. An autopsy was promised, but the doctor was out of town when the patient died, and his assistant failed to obtain the postmortem.

ANATOMY OF THORACIC DUCT. The thoracic duct extends from the second lumbar vertebra, where it originates, to the junction of the internal jugular and left subclavian veins, where it terminates. It is the common collector of all the lymphatic vessels of the subdiaphragmatic portion of the body, and, moreover, frequently, but not invariably, receives the left jugular, subclavian, and internal mammary trunks, which bring the lymph from the left supradiaphragmatic portion of the body.

Course, direction. It is rare for the duct to arise below the second lumbar vertebra. Its origin is, however, often situated on the first lumbar or even on the twelfth dorsal. It runs at first vertically upward, passing a little to the right of the midline. Then from the sixth to the fourth dorsal it changes its direction and runs obliquely upward and to the left, in this manner crossing the anterior surface of the vertebral column in a slanting direction and continuing its ascending course as far as a horizontal line drawn through the lower border of the sixth cervical vertebra. At this point it quickly changes its direction, describes a curve with the concavity downward, and runs downward, outward, and forward and terminates in the venous junction. Its caliber varies in different parts. At its origin it has a dilated portion generally termed reservoir or cistern or pecquet (receptaculum chyli). It is in the middle part of its course that the duct is least developed, measuring only 4 to 6 mm. in diameter. At its termination there is a dilatation represented by Mascagni and called the ampulla.

PHYSIOLOGY. The physical and chemical properties of chyle vary at different times and under various circumstances; the most important factor determining its properties is, however, the character of the food in the intestinal canal. Most of the knowledge of the character and composition of chyle has been derived from experiments on the lower animals, especially the dog, in which animal it is not difficult to insert a cannula into the thoracic duct where it joins the left subclavian, at the root of the neck. Unfortunately this fluid is not pure chyle, but consists of a mixture of chyle and lymph coming from the lymphatics of the liver, kidneys, pelvis, abdominal wall, lower extremities, etc.

Chyle when a mixed diet is given is a white opaque fluid, occasionally colored slightly red or yellow from the accidental presence of red-blood corpuscles. In herbivora it may have a greenish tinge from the chlorophyl derived from the food. Reaction is alkaline, due to carbonates and phosphates of sodium. Sp. gr., 1018 to 1025. Salty taste and odor (due to volatile, fatty acids) peculiar to the animal from which it is derived. It coagulates on standing sometimes more and sometimes less readily. Microscopically it contains leukocytes and fat granules, the latter having a peculiar Brownian movement.

Chyle obtained from the lacteals before they pass through lymph glands is found to contain fewer leukocytes than that from vessels which have passed through these glands. A constant stream of leukocytes thus passes from the chyle into the blood. This is an important source of the leukocytes of the blood.

CHEMICAL ANALYSIS (MUNK) IN MAN.

One hundred parts.	Chyle.	Lymph.
Water	92.2	95.2
Solids	7.8	4.8
Fibrin	.1	1.
Proteids	3.2	3.5
Fats, lecithin, and cholesterin	3.3	traces
Extractives	.4	.4
Salts	.8	.8

This table shows very clearly that chyle differs from ordinary lymph in but one important point, viz., in containing a larger percentage of fat.

In exceptional cases chyle contains a larger percentage of sugar than does lymph. Chyle differs from serum in two important particulars: it contains a larger percentage of fats, but a smaller percentage of proteins than does blood serum. The amount of urea in chyle is, according to Gehant and Quinquaud, greater than in the blood.

Munk and Rosenstein (to whom we are indebted for nearly all of our knowledge of the absorption of fat in man) had the opportunity of observing and experimenting upon a girl who, as a result of elephantiasis of one leg, had a fistula in the thigh which communicated through the left lumbar lymphatic duct with some of the lacteals. It was found that when fat was given to the patient two-thirds of it could be recovered from the fluid escaping from the fistula in the following twelve hours; further examination of the blood showed no more fat to be present than when the patient was fasting.

The soaps in chyle amount to 0.2 per cent. The fat in chyle is almost entirely in the form of neutral fats. The fat granules are less than 1 μ in diameter and show Brownian movement.

When large amounts of sugar are fed, some may be absorbed by the lacteals and appear in the chyle, but not so with protein. On the other hand, Asher and Barbera found that when a very large amount of protein was introduced into a dog's stomach as much as 6.4 per cent. of it could be recovered from the chyle.

Noel Paton observed the flow of lymph from the thoracic duct in a case in which the duct had been injured during an operation for sarcoma of the neck. He estimated the normal amount to be 130 to 195 c.c. per hour. His patient, however, was not in normal condition.

Munk and Rosenstein found from 70 to 120 grams of chyle escaped per hour from the fistula before and 150 grams after a meal. This was not pure chyle but a mixture of chyle and lymph.

The force exerted upon the contents of the thoracic duct by the passing current of blood in the subclavian is nothing more than an illustration of the hydraulic principle of Venturi, *i. e.*, if a stream is made to flow through a tube into which another opens and communicates at its distal end with a reservoir of water a current will be established in the second tube and will continue as long as the stream flows through the first tube or any fluid remains in the reservoir of the second. The anatomical junction of the thoracic duct with the venous system is peculiarly favorable to the maximum development of this principle, for the near affluence of the internal jugular and the downward inclination of the duct to the subclavian, contribute to enhance the effect upon the current of chyle. Out of this principle of Venturi must grow the converse, that any retardation of or obstacle to the current of blood in the subclavian vein, either from diminution of its lumen or from regurgitant heart affections, must slow the movement of the chyle in the duct and in its tributaries. Hammersfahr discusses the question of the permeability of the pleura to chyle, and concludes that the intact pleura is permeable.

Morton performed a number of experiments upon dogs by ligating the thoracic duct; in some the receptaculum and in others the lacteals burst. In every case there was extravasation of chyle.

In Sir Astley Cooper's experiments when rupture occurred it took place at the receptaculum, and Dupuytren's experiments on horses were followed by similar results. Cooper says it is not necessary to tie the duct. If the animal is fed with milk and the extremity of the duct compressed one-half hour afterward the receptaculum will rupture.

Busey quotes from Niemeyer's text-book of *Practical Medicine* as follows:

"Obstructive engorgement of the great veins extends also to the thoracic duct. When the subclavian vein is filled to distention the flow of chyle and lymph must encounter a resistance equal to that opposed to the current of any other vessel which empties into the subclavian. Nay, if lymph be the source of the fibrin of the blood we see, upon simple physical grounds, why the blood of emphysematous patients is poor in fibrin, why the venous crasis presents hyperinosis and increase of fibrin. Restricted afflux of chyle must, moreover, prejudice the nutrition both of the blood and of the entire organism. It is one of several causes which contribute to the general emaciation and to the premature marasmus of the emphysematous persons; perhaps too it may account for the lack of albumin in the serum, which produces a tendency to the establishment of dropsical symptoms."

He also quotes Hertz as follows:

"The inadequate emptying of the thoracic duct into the left subclavian vein overdistended with blood will in cases of pulmonary emphysema lead to impoverishment of the blood insofar as concerns such elements as are derived from the lymph, the colorless blood corpuscles, fibrin and albumin."

This explains very well the fact that after one of the inguinal glands was removed from our patient there was considerable oozing of blood from the wound even on the fifth and sixth days.

Schmidt-Mulheim tied the thoracic duct of a dog in a most complete manner, securing also the cervical and both subclavian veins. On the sixth or seventh day the dog, in excellent condition, was killed and milky fluid was found around the thoracic duct and in the chest and abdomen. No rupture of the duct could be made out.

In the 47 cases collected by Baldwin the age incidence, where age was noted, was:

Under 10 years	2 cases
11–20 "	8 "
31–40 "	7 "
41–50 "	8 "
51–60 "	3 "
60 + "	2 "

The average age was thirty-six years. The greatest number occurred between eleven and fifty-one years. Of all cases of milky fluid in the chest collected up to 1900, 54 in all, 31 were chylous, 13 chyliform, and 10 doubtful. In 41 true cases in which sex was given, 31 were males and 10 females. Sale's patient was a male, as was ours.

The causes as given in 47 cases were as follows: 16 from chest injury; 9 from pressure exerted upon the duct by new growths outside the duct or by tuberculous lymph nodes; 9 from secondary growths in the duct; 4 from thrombosis of the left subclavian vein; 2 from proliferating lymphangitis; 2 from aneurysm-like dilatation of the duct; 1 from thrombosis of duct; 1 occurred during an operation for removal of carcinomatous lymph nodes of the neck; 1 was due to obstruction of the radicles of the duct from inflammatory thickenings in the mesentery; 1 from mitral disease; 1 from filaria.

Simon records a case in which a lymphangioma of the leg reached the thorax and burst into the pleura.

All of these causes produce either a break in the continuity of the endothelial lining of the duct or put the endothelial cells under such abnormal conditions that their nutrition is impaired and consequently they allow the transudation of chyle.

The symptoms of chylothorax which result directly from the condition are not characteristic. They are those of hydrothorax or pleural effusion. In most cases the chief and at times the only symptom is a gradually increasing dyspnea. In fatal cases this may be accompanied by a rapidly progressing emaciation, although the patient may have a good appetite and eat well. A few patients complain of pain in the affected side if the condition is unilateral and of a general indefinite dull pain in the chest if bilateral. There is lagging of the affected side and more or less obliteration of the intercostal spaces. If the quantity of fluid is large there may be considerable displacement of the heart. Palpation reveals lessened or absent vocal fremitus, depending upon the amount of fluid. Percussion gives a dull note on the affected side laterally and behind, the line of dulness being higher in front and lower in back when the patient is sitting and reversed when in a recumbent position.

Edwards says 60 per cent. of cases occur on the right side.

In 17 of 47 cases there was an accompanying chylous ascites; in 1 chyluria: in 1 milky diarrhea. Bayer collected 20 cases of combined chylothorax and chylous ascites.

Edwards, in 1901, was able to collect only 2 cases of chylopericardium; 1 from leakage of chylous fluid from the pleura; the other from rupture of chyle vessels.

The diagnosis of chylothorax, as noted above, is made by paracentesis. The fluid is usually semitranslucent, milky, and opalescent, of alkaline reaction, and sp. gr. about 1020. If allowed to stand it separates into two layers: an upper, cream-like in consistence, and a lower layer watery in character. If the whole is well shaken and extracted with ether or treated with sodium or potassium hydroxide the fluid loses its milkiness and becomes clear. Chemical examination shows 90 to 99 per cent. water and 0.02 to 0.92 per cent. fat.

Sale, in 1913, reported a case of chylothorax in a man who was living and doing well six months after the condition was diagnosed and treated. The blood in his case contained 95 per cent. hemoglobin; red-blood cells, 4,900,000; white-blood cells, 4800; large polymorphonuclears, 62 per cent.; lymphocytes, 32 per cent.; mononuclears and transitionals, 4 per cent.; eosinophiles, 1 per cent.; mast cells, 1 per cent. In attempting to explain the pathology in his case he says:

"There may very well be a tumor, *e. g.*, tuberculous or luetic gland, exerting pressure on the left subclavian vessels, diminishing the pulse wave in the left radial and at the same time retarding the flow of and damming back the chyle in the thoracic duct. It may be necessary further to assume that the thoracic duct runs upward through the mediastinum to the right of the azygos vein and in close juxtaposition to the right pleura, as indeed sometimes happens."

In 1907 Dock reported a very interesting and instructive case, viz., in 1902 diagnosis of abdominal tumor was made by Prof. de Nancrède. Soon after many glands enlarged in the neck, groins, and axillæ. In 1906 the abdomen began to enlarge until the waist measured sixty inches. Great dyspnea. A grating sensation in the abdomen was audible to others as well as to the patient.

Under treatment by salines for six weeks waist measurement was reduced to thirty-six inches. The abdomen was aspirated twice and 6 and 9 quarts of pink, opaque, milky fluid were removed. One year later 6 liters of similar fluid were removed. Blood-pressure: systolic, 100 to 104; diastolic, 55 to 62. One axillary gland removed for examination.

Dr. Warthin's report: Lymphocytoma (lymphosarcoma); aleukemic stage?

Autopsy. Thoracic duct: extending from receptaculum chyli to subclavian vein is a solid cord of tissue, larger below, where it is about 4 to 6 cm. in diameter, gradually decreasing above to 2 cm., filling up the greatly dilated thoracic duct. On section it is pale with scattered reddish spots, medullary uniform consistence; very cellular, resembling the abdominal tumor and the lymph glands in all respects. Above the tumor mass projects slightly into the subclavian vein. Below the large mass in the receptaculum chyli is directly connected with the retroperitoneal and mesenteric mass of cords of similar lymphoid tissue.

Blood: white-blood cells, 625 cells counted; lymphocytes, 69.8 per cent.; large mononuclears and transitionals, 7 per cent.; polymorphonuclears, 27.4 per cent.; eosinophiles, 1.3 per cent.; basophiles, 3 per cent.; normal small lymphocytes, 1 per cent.

Sediment of ascitic and pleural fluid shows lymphocytes almost exclusively. Sternum easily fractured and red marrow hyperplastic.

Prognosis. The prognosis in many cases may be good. In those due to obstruction the anastomosis, which occurs only high in the chest, may do compensatory work and relieve the condition. Internal rupture of the thoracic duct is not always fatal. In cases due to injury to the duct from external causes proper treatment frequently brings about a cure. Handmann cites the following case:

A man had his chest caught between the drive wheel of a steam engine and a wall. He was taken to the hospital, where the left clavicle and several ribs were found to be fractured. Two days later effusion was discovered in the left pleura. Exploratory puncture yielded milky fluid of a rosy color. Chemical and microscopic examination showed the presence of chyle mixed with blood. Ten days later the red corpuscles had disappeared and the effusion had the appearance and composition of pure chyle. Absorption took place without complications and the patient recovered fairly rapidly.

Treatment. The treatment of chylothorax depends entirely upon the cause. In those cases due to chronic obstruction, aspiration, rest in bed, and nourishing food are indicated. A word of caution in regard to paracentesis: Do not remove too much at one time, because (1) of the disturbance of balance of the circulatory pressure, and (2) when the pressure exerted by the fluid is released it favors the exudation of more fluid. Erb described a case of lymphangiectasis of the thoracic duct with chyle in the right pleural cavity in which the patient lived two months, was tapped eight times and lost twenty-five liters of chyle.

Cases due to chest injury are treated similarly. Where the cause is injury during operation, as for removal of carcinomatous or tuberculous lymph nodes in the neck, the duct may be ligated, resected, or packed.

To sum up our case, it is probable the pathology is as follows: The patient developed lymphosarcoma of the mesentery. Metastasis occurred in the inguinal, axillary, and abdominal wall lymph glands and in the thoracic duct. The tumor growing in the duct, or metastases in the mediastinal lymph glands caused obstruction, partial or total, of the duct with consequent transudation of chyle into the pleural cavities. The blood in the specimen was probably due to hemorrhage from the tumor.

CONCLUSION. In conclusion, I wish to express my appreciation of Dr. Preble's kindness in permitting me to report this interesting case, and to those whose names are mentioned in the paper, my sincere thanks.

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THE ENERGY INDEX OF THE CIRCULATORY SYSTEM.

By Joseph H. Barach, M.D.,
PITTSBURGH, PENNSYLVANIA.

Various methods of estimating the work of the heart and circulatory efficiency have been proposed from time to time. Some were based upon experimental and laboratory proof, others upon clinical observations, and yet out of the many there is not one that is generally accepted as being better than the rest. All of which, I believe, goes to show that up to the present time, for clinical purposes, the problem has not been approached from a correct stand-point, and has not been solved.

Strassburger[1] believed that the pulse pressure divided by the systolic pressure indicates the vascular resistance and the work of the heart. His far-reaching conclusions, however, were opposed by Sahli.[2]

Tigerstedt[3] proposed the formula P.P.MP.R. velocity, and the P.P.MP.R. efficiency of the heart as a pump.

This formula is the same as Strassburger's, and, therefore, has the same limitations.

In 1911 Goodman and Howell,[4] following the work of Tornai[5] and of Fisher,[6] constructed a formula based upon the assumption that the first and fourth phase of the auscultatory method indicates cardiac weakness, and the second and third phase indicate cardiac strength. Their method consisted in determining the percentage relation of the C. W. phase and the C. S. phase to percentage of the pulse pressure. If the C. S. were greater than the C. W., then compensation was considered good, and *vice versa*. The method has been applied clinically and found wanting.

In 1913 Stone[7] proposed a method of estimating the heart's work. The assumption of Stone was that normally the pulse pressure constitutes 50 per cent. of the D. P., and that whenever the pulse pressure is over 50 per cent. of the D. P., then the increment represents cardiac overload.

I show here that in a series of 742 normals the P. P. may constitute anywhere from 20 per cent. to 80 per cent. of the diastolic pressure in 80 per cent. of the cases; and while the average of the figures is 50 per cent., yet it does not at all hold true that in the normal person the P. P. equals 50 per cent. of the D. P.

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[1] Arch. f. klin. Med., 1905, lxxxv.

[2] Mānch. med. Wchnschr., 1903, No. 47.

[3] Swan, John M., Arch. Int. Med., February 15, 1915, xv, No. 2, p. 269.

[4] Ibid. [5] Ibid. [6] Ibid.

[7] Clinical Significance of High and Low Pulse Pressure, with Special Reference to Cardiac Load and Overload, Jour. Am. Med. Assn., October 4, 1913, p. 1256.

TABLE I.—RELATION OF PULSE-PRESSURE TO DIASTOLIC PRESSURE IN SEVEN HUNDRED AND FORTY-TWO NORMAL PERSONS.[8]

5 to 10	2			
10 to 20	18			
20 to 30	68			
30 to 40	111			
40 to 50	122	249 cases	461 cases	597 cases
50 to 60	127	33%	62%	80%
60 to 70	101			
70 to 80	68			
80 to 90	55			
90 to 100	25			
100 to 110	29			
110 to 120	3			
120 to 130	3			
130 to 170	10			
Total	742			

We may note that the greatest number of cases do occur near the 50 per cent. mark, and if we were to strike an average it would be close to 50 per cent., yet this would be far from representing the actual truth. These tables show there is a wide range both above and below the 50 per cent. mark in normal individuals. Our findings here warrant only a statement that the pulse pressure equals from 20 to 80 per cent. of the diastolic pressure in about 80 per cent. of the cases. And this is where we stand today. Certainly it cannot be said that any of the above methods have withstood critical investigation. There is no known method which satisfactorily indicates the amount of work which the heart or the cardiovascular system is performing; nor when the work thrown upon the circulatory system is becoming greater than its functional capacity. Nor do we have a means of measuring accurately the total work of the circulatory system and the amount of energy expended in the performance of that work. It seems, then, that we must approach this problem by another route; and such is my present purpose.

In 1914 I[9] presented a method of estimating the activity of the cardiovascular system. The purpose of this method was to indicate the expenditure of energy by the circulatory system in the act of maintaining the circulation, and it was based upon a calculation made from the three measurable factors of the arterial circulation. I wish to emphasize the fact that in this method we are dealing only with measurable factors and not inferences, such as velocity, work of the heart, functional capacity, etc.

However much one's experience may have taught him of the condition of the circulatory system, of the degree of its activity, and of its efficiency, nevertheless the all-important clinical evidences relative to the arterial circulation which one may record for the understanding of another are the systolic and diastolic pressures and the pulse rate.

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[8] Barach and Marks, Blood-pressures, Arch. Int. Med., April, 1914, xiii, 648–655.

[9] Barach, Joseph H., The Energy Index, Jour. Am. Med. Assn., February 14, 1914, lxxii, 525.

When we go beyond these evidences in attempting to measure such activities as the blood flow, the cardiac output, functional capacity of the heart, the cardiac load, etc., we find ourselves in the realm of speculation. And while it would be highly desirable indeed to be able to make such measurements, nevertheless it has been amply proved that our present-day methods are insufficient for such purposes.

MEASURABLE FACTORS IN THE CIRCULATION. At the present time our clinical methods are almost entirely limited to the determination of the systolic and diastolic pressure and the pulse rate, and these observations may be made with a minimum of apparatus and technic. With the mercury manometer and by the auscultatory method we can determine the values of these three factors with certainty and accuracy.

Much has been said and written of the pulse pressure; it has been used as a basis for calculation of the blood flow, the work of the heart, cardiac load and overload, etc.; but after numerous observations of my own and a *résumé* of the work done by others, I am inclined to believe that up to the present time at least the estimation of pulse pressure has added comparatively little to our total knowledge of the circulation. I do believe that we will still gather some facts by studying the pulse pressure under certain conditions, but up to the present this has not yet been accomplished. The important factors are the systolic pressure which indicates the ventricular force, the diastolic pressure which indicates the intravascular tension during diastole, and at the same time the peripheral resistance, and the pulse rate which designates the frequency with which the heart must contract to maintain the flow of blood as required by the organism. It may be stated as an axiom that no alteration in function of the circulatory system can take place, but there is a change of values or a readjustment in more than one of the three factors. These three factors are interdependent, one upon the other, and are constantly adapting reciprocally to one another according to the needs of the organism. The relation of systolic and diastolic pressure and pulse rate, one to the other, may well be illustrated by comparison to a triangle of fixed area in which if one line of the triangle is altered the other two are likewise changed. I illustrate this by shaping a piece of cord or a chain in the form of a triangle, by which is readily seen that changing the length of the base or either one of the sides of that triangle alters the value of the other two sides.

ADAPTATION OF MAXIMUM AND MINIMUM PRESSURES AND PULSE RATE. That there is a constant adaptation of each factor in the triad to the others is shown in the following results obtained from a series of 24 cases. These observations were made in young men previous to a race of 24.85 miles. The young men were in extraordinarily good physical condition. We found that change of posture from horizontal to erect caused an increase of pulse rate in 14, a diminution in 4 and no change in 6. The maximum pressure was diminished in 11, unchanged in 3, and increased in 10. The minimum pressure was diminished in 9, unchanged in 9, and increased in 6. After the race, in which 19 out of the 24 finished, when the blood-pressure had fallen fully 20 per cent., and the subjects were in a state of exhaustion, upon change from horizontal to erect posture the pulse rate was increased in 18 and unchanged in 1. The maximum pressure was diminished in 11, unchanged in 3, and increased in 5. The minimum pressure was diminished in 7, increased in 6, unchanged in 4, and not obtained in 2.

The conclusions from the above observations are that whether the vascular tone be of the highest attainable state of efficiency or in a state of exhaustion, each element in the triad is a constantly varying factor, and that whether the cardiovascular tone be good or poor, the manner of reaction appears to be the same, at both times being accomplished by a readjustment of all the factors. It appears, therefore, that these observations bear out the previously stated axiom.

Adaptation of the Triad in Cardiac Hypertrophy. Another example of the accommodation of these factors, one to the other, is to be found in the following figures based upon observations in a series of athletes who presented the pure form of cardiac hypertrophy—the athletic heart. In this series of cases in which we knew that the left ventricle was enlarged because of its appearance behind the fluoroscope and by physical examination, and in which the systolic pressure was increased, we found that the pulse rate was slower than in a series of subjects who had not undergone systematic physical training. Whereas, in a series of cases in which the maximum pressure ranged between 100 and 120, the average pulse rate was 79 in 29 non-trained men and 76 in 12 trained men. In a series in which the maximum pressure ranged from 130 to 140 the pulse rate was 82 in 22 non-trained men and 72 in 7 trained men.

From this we see that when the left ventricle becomes hypertrophied and the ventricular force and output are greater, the conserving forces of the body will cause a slowing of the pulse rate.

By a slowing of the pulse rate the total expenditure of energy per unit of time in the hypertrophied heart was not greater than in the non-hypertrophied heart. As measured by the S. D. R. index the average energy expenditure in the 100 to 120 non-hypertrophied cases was 15,908 mm. Hg. per minute, and in the hypertrophied cases 15,706 mm. Hg.

In the cases in which the maximum pressure ranged from 130 to

140 mm. Hg. the energy index of the non-hypertrophied cases was 17,960 mm. Hg. and 16,856 mm. Hg. in the hypertrophied cases, showing that whether the heart is hypertrophied or not, the normal organism requires but a certain fulfilment of function, and that the hypertrophy is necessary only for the occasion of greater effort. Along with the other features which this method of calculation seems to bring out, these foregoing evidences point clearly to the fact that if we are to come to a correct conclusion as to the activity of the circulatory system we must take into our calculation the complete triad.

The S. D. R. Index. Since the evidences upon which we may depend are included in the triad formed by the systolic pressure, diastolic pressure, and pulse rate, it seems that a calculation based upon this triad must give us the desired information relative to the activity of the arterial circulation. Such is the purpose of the S. D. R. index.

The premise here is that each pulse beat is composed of two successive phases—the systolic phase and the diastolic phase—and that the total force exerted with both phases is what constitutes the entire beat. The systolic pressure in an artery is that amount of force exerted with the systole which is capable of lifting a column of mercury to a certain height. The diastolic pressure is the force exerted by the intravascular tension during the diastolic phase. For example, in a certain case the systolic force (kinetic energy) is equal to the lifting of 120 mm. of Hg. and the diastolic force (kinetic energy) is equal to 80 mm. of Hg. pressure. Therefore, with one pulse beat the measurable quantity of force (kinetic energy) is equal to the lifting of 200 mm. Hg., and with 72 such pulse beats the force would be 72 × 200 or 14,400 mm. Hg.

For clinical interpretation we may presume that the systolic pressure represents the effort of the arterial system, and the pulse rate represents the effort of the heart, as a whole, to maintain the circulation. Or we may assume that we are simply trying to determine the degree of effort expended by the circulatory system in carrying on the circulation to maintain the needs of the organism. For that purpose we note the energy of the systole, of the diastole, and how many times per minute that much energy is expended. We do not deal here with absolute results, the product of our calculation does not quantitatively measure, but it does indicate clearly the expenditure of energy per unit of time.

The Normal S. D. R. Index. If we are to use this method of estimating the energy expenditure per unit of time we must establish the values of normal persons. For that purpose the following table has been constructed. This table is based upon 250 normal individuals in whom the pressure ranged within what we consider the extremes of normal limits. Here are included only those cases in which the minimum pressure did not exceed 100 mm. Hg. and the pulse rate did not exceed 90 beats per minute. With an upper limit of about 150 mm. Hg., I believe we are within the normal bounds.

TABLE II.—TOTAL ENERGY INDEX IN TWO HUNDRED AND FIFTY NORMAL PERSONS.

100	3	cases average	13541	mm. Hg.	per minute
100 to 120	42	“ “	15918	“	“
120 to 130	123	“ “	16902	“	“
130 to 140	44	“ “	17690	“	“
140 to 150	22	“ “	18527	“	“
150 to 160	16	“ “	21076	“	“
	250				

I therefore believe that in normal persons, as estimated by the energy index, that the pressure does not exceed 20,000 mm. Hg. per minute.

Variations in Energy Expenditure as Detected by the Index. Here it is my purpose to show that the maximum pressure reading alone conveys practically no information concerning the activity of the circulation.

The following table is based upon observations made upon a group of 289 young men between the ages of fifteen and thirty years. I have chosen the extreme cases of each group, and show that while Case A and Case Z both had the same maximum arterial pressures, the total energy expenditures at the time of examination was very much greater in Case Z than in Case A. This difference of activity in the circulation of these cases was quite obvious. Some of these young men entered the examination room anxious-looking, pale, with apex impact prominent, and at first glance it could be seen they were in a state of mental and nervous excitation with the usual effects upon the cardiovascular system.

The energy index in these cases showed this increased action, whereas the maximum pressure reading indicated nothing of what was actually going on at that time.

TABLE III.—TABLE OF TOTAL ENERGY INDEX IN TWO HUNDRED AND EIGHTY-NINE CASES.

Group.	No. of cases.	Maximum blood pressure, mm. Hg.	Extreme instances. Case.	Maximum.	Minimum.	Pulse.	Energy index, mm. Hg. per min.
1	41	From 110 to 120 .	A	115	52	72	12.024
			Z	110	88	124	24,552
2	99	120 to 130 .	A	124	68	68	13,056
			Z	125	100	120	27,120
3	76	130 to 140 .	A	138	90	64	14,592
			Z	132	118	132	33,000
4	43	140 to 150 .	A	142	85	60	15,436
			Z	148	98	120	29,520
5	26	150 to 160 .	A	150	90	76	18.240
			Z	150	115	88	27,440
6	4	160 to 170 .	A	164	110	68	18,632
			Z	162	80	120	29,040

EFFECT OF PHYSICAL EXERTION AS INDICATED BY THE S. D. R. INDEX. During the past year, with the assistance of Dr. W. L. Marks, of the Carnegie Institute of Technology, I made a rather extensive series of observations upon the effect of graduated amounts of physical exertion upon the circulatory system and calculated the results by the S. D. R. index. This work will be published later in detail, but for the present purpose I cite an instance of the results obtained. The exercise consisted of running to the time of a metronome at the rate of 152 steps per minute for a period of one minute:

	CASE A.				CASE B.			
	Pulse.	Systolic.	Diastolic.	Index, mm. Hg.	Pulse.	Spstolic.	Diastolic.	Index, mm. H6.
Before . . .	72	104	78	13,104	100	120	85	20,500
15 seconds after	92	132	90	20,424	132	165	95	34,320
5 minutes after	80	120	80	16,000	108	130	90	23,760

These figures in all cases show (1) that each one of the triad is a constantly varying factor; (2) they show that with the exertion there came an increased demand upon the circulatory system, and that as this demand ceased the activity lessened and returned toward the normal, sooner in some cases than in others, and finally the figures show the degree of reaction on the part of the circulatory system.

By observing the effects of definite amounts of physical exertion upon the circulatory system, as indicated by the S. D. R. index, and by noting the degree and duration of the increase, we have come upon a method of estimating the circulatory efficiency of our subjects. This we will treat fully in a later consideration of this subject.

SUMMARY. 1. It is an axiom that changes in the activity of the circulatory system are accomplished by the adjustment of three factors: the maximum pressure, minimum pressure, and pulse rate.

2. That since these are measurable factors a calculation based upon this triad should indicate the tótal energy expenditure of the circulatory system.

3. The product of such a calculation, which I termed the energy index, under normal conditions represents a kinetic force per minute equal to not over 20,000 mm. Hg. pressure.

4. In the S. D. R. index or the energy index we have a method which is based upon the three measurable factors of the circulation, and one which indicates per unit of time the total expenditure of energy by the circulatory system in the performance of its functions.

THE BLOOD-PRESSURE IN PNEUMONIA.

By Frederick Tice, M.D.,
CHICAGO, ILLINOIS.

(From the Eighth Medical Service of the County Hospital, Chicago.)

From a clinical stand-point the mode of death in pneumonia is of the greatest importance. On this determination the prognosis and treatment must necessarily in greater part depend. It is safe to say that the larger number of clinicians will accept the statement of von Jürgenson that, "Patients who die of pneumonia are killed by cardiac insufficiency."

The factors assigned in producing the cardiac failure are (1) the pneumonic exudate interfering with and obstructing the pulmonary circulation, thus increasing the work of the right heart; (2) the pneumonic changes in and about the lung resulting in a disturbance of the normal pulmonary influence in maintaining the circulation and (3) the injurious effects of the fever on the heart.

One of the important problems in the study of pneumonia is that associated with the causative factors of the cardiac failure.

The slight mechanical influence on the lesser circulation and the interference of the respiratory assistance to the circulation can hardly be seriously considered, especially when a small localized consolidation produces a fatal outcome or an enormous, perhaps, complete involvement of one entire lung, goes on to a favorable termination. Even the myocardial degeneration described by von Jürgenson, Zenker, and Liebermeister as due to the pyrexia was brought into question by Aufrecht when he directed attention to cardiac failure in pneumonia with slight fever and the infrequent occurrence of the same in diseases with long-protracted fever, as in typhoid.

However, it must be admitted that pneumonia patients die and the fatal termination is usually manifest by signs and symptoms of circulatory failure. At present it is generally admitted that the circulatory disturbance is produced by the pneumococcal toxemia, but how or in what manner has not been definitely determined.

Admitting that the fatal issue is brought about by a circulatory failure, the result of the toxemia, it is evident that some portion of the cardiovascular apparatus must be involved. For practical purposes this means anatomical or functional changes in either the heart or the vascular system, including the contained blood, while, undoubtedly, in some instances there is a simultaneous involvement of the entire circulatory apparatus.

Regardless of a few exceptions, it was formerly quite generally accepted that the myocardium was at fault, until Romberg[1] and his associates investigated the problem experimentally and arrived at the conclusion that the circulatory failure invariably followed an exhaustion or paralysis of the vasomotor center in the medulla. Since that time up to recently the vasomotor theory has held full sway, to the complete exclusion of the previously accepted idea of myocardial degeneration.

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[1] Experimentelle Untersuchungen über die Allgemeine Pathologie der Kreislaufstorung bei Acuten Infectionskrankheiten, Arch. f. klin. Med., 1899, lxiv, 652.

However, as might be expected, recent experimental and clinical investigation has again emphasized the importance of the cardiac involvement and with a corresponding diminution of the influence of the vasomotor mechanism.

Newburgh and Minot,[2] in their clinical study of pneumonia, among other findings, arrived at the conclusion that the blood-pressure curve did not suggest a failure of the vasomotor center. This conclusion has been amply confirmed experimentally by W. T. Porter and L. H. and I. Newburgh.[3] They were able to demonstrate that the vasomotor center was not impaired in fatal pneumonia.

Even more convincing are the microscopic findings of Willson,[4] as determined in the fatal pneumonias. In every instance he was able to detect myocardial changes due either to a toxemia or a local infection. That it could be otherwise is hardly to be expected, when it is recalled that fatal pneumonia is accompanied by a toxemia and practically every case with a pneumococcal septicemia.

With the evidence at hand it is apparent that no definite and final statement can be made, further than fatal pneumonias die with the clinical manifestations of a circulatory failure, the result of a pneumococcal toxemia and septicemia; but whether the myocardium or the vasomotor apparatus is chiefly involved remains in doubt. Perhaps it may be ultimately determined that there are various groups in which one or the other predominates, while in some, both the myocardium and vasomotor system are concerned.

On the experimental findings of Romberg and his associates,[5] G. A. Gibson[6] formulated a statement in reference to the relation of the blood-pressure to the pulse-rate, known as the Gibson rule, which is as follows: "When the arterial pressure, expressed in millimeters of mercury, does not fall below the pulse-rate, expressed in beats per minute, the fact may be taken as of excellent augury, while the converse is equally true. From the work of the last few years in my own wards no fact is more certain than this."

During the past few months a careful clinical study of the application of this rule has been made of the pneumonias admitted to the Ward Eight Medical Service at the County Hospital. In each instance a careful record was made of the pulse, temperature, and respiration rate every four hours. The systolic blood-pressure, by the auscultatory method, was determined at least every twelve

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[2] The Blood-pressure in Pneumonia, Arch. Int. Med., 1914, xiv, 48.

[3] The State of the Vasomotor Apparatus in Pneumonia, Am. Jour. Physiol., 1914, xxxv.

[4] The Heart in the Pneumonias, Jour. Am. Med. Assn., 1914, lxiii, 981.

[5] Loc. cit.

[6] Some Lessons from the Study of the Arterial Pressure, Edinburgh Med. Jour., 1908, n. s., xxiii, 17

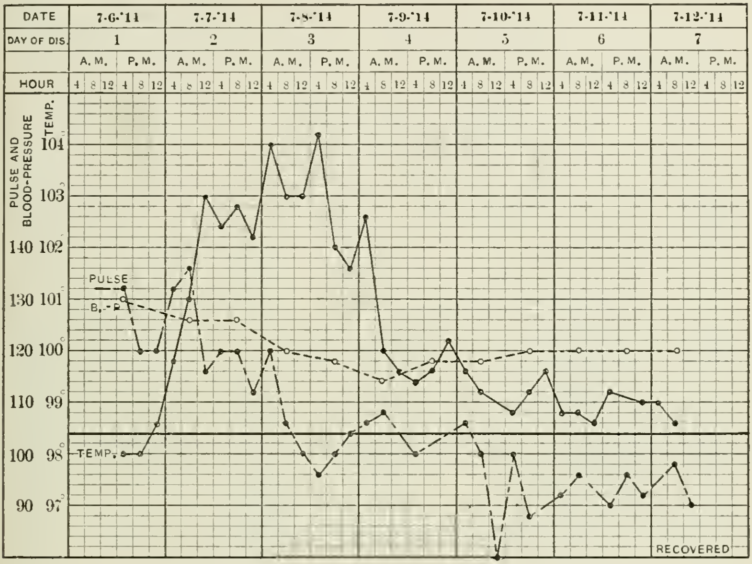

Chart I.—Chart from a case of pneumonia with recovery, showing blood-pressure well above pulse-rate.

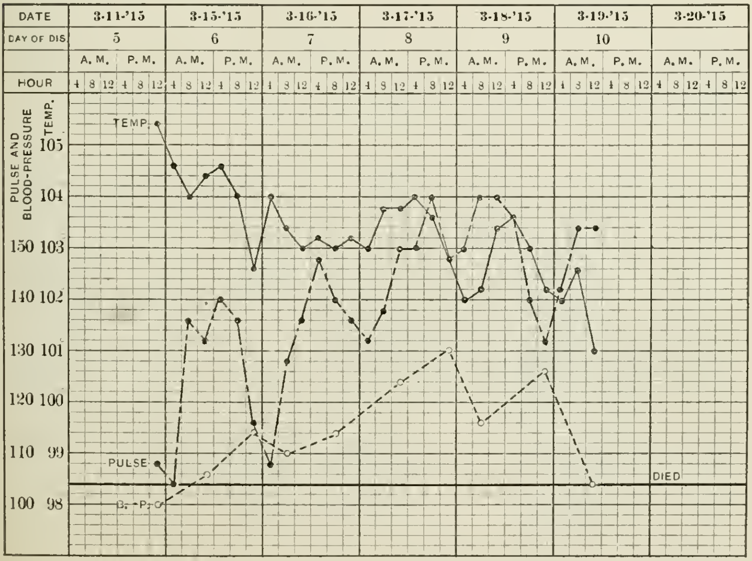

Chart II.—Chart from a fatal case of pneumonia in which blood-pressure fell far below pulse-rate.

hours. From these records a chart was made showing the pulse-rate and blood-pressure curves. For convenience the temperature curve as well as the time and amount of digitalis administered, were also included. The number of pneumonias so charted includes 31 cases, which may be divided, for further study, into two groups according to the relative position of the blood-pressure above or below the pulse-rate.

GROUP 1—BLOOD-PRESSURE CONSTANTLY, OR IN GREATER PART, ABOVE THE PULSE-RATE.

No.	Name.	Age.	Involvement.	Leukocytes.	Day of illness.	Complications.	Result.	Gibson rule.
1	M. M.	39	Left lower	14,000	4	Mitral insufficiency Nephritis	Died	Negative.
2	O. E.	44	Right lower	8,128	4	Mitral insufficiency	Recovered	Positive.
3	D. N.	39	Left lower	...	3	....	Recovered	Positive.
4	M. G.	29	Left lower	19,350	2	....	Recovered	Positive.
5	M. R.	44	Right upper	19,400	4	Mitral insufficiency	Recovered	Positive.
6	M. M.	24	Right lower	14,000	?	....	Recovered	Positive.
7	F. S.	63	Both lower	24,000	7	Myocarditis Nephritis	Died	Negative
8	E. C.	48	Left lower and upper	29,300	6	....	Recovered	Positive.
9	V. C.	27	Right lower	11,700	1	....	Recovered	Positive.
10	T. T.	23	Left lower	14,000	7	....	Recovered	Positive.
11	S. G.	58	Left lower	80,000	3	Myocarditis Obesity	Died	Negative.
12	V. M.	21	Both lower	20,000	4	Pleurisy	Recovered	Positive.
13	A. McD.	48	Right lower and middle	14,000	5	Nephritis	Recovered	Positive.
14	M. M.	56	Left lower (complete) Left upper (partial)	33,800	?	Pleurisy Dilated heart	Died	Negative
15	H. E.	70	Right lower	31,300	6	Nephritis Myocarditis	Died	Negative.
16	M. E.	43	Right lower	17,700	5	Bilateral pleurisy	Recovered	Positive.
17	E. C.	64	Left upper	27,800	6	....	Recovered	Positive.

Summary: Of the 17 cases, 12 complied with the rule, or 70.5 per cent.

GROUP 2—BLOOD-PRESSURE CONSTANTLY, OR IN GREATER PART, BELOW THE PULSE-RATE.

No.	Name.	Age.	Involvement.	Leukocytes.	Day of illness.	Complications.	Result.	Gibson rule.
1	J. K.	38	Right lower and right upper	...	5	....	Recovered	Negative.
2	T. W.	49	Left lower	20,500	7	Nephritis	Died	Positive.
3	L. S.	19	Both lower	15,000	8	Pleurisy	Recovered	Negative.
4	M. L.	61	Both left and right upper	14,250	?	....	Died	Positive.
5	A. M. R.	41	Right upper and middle	26,250	8	....	Died	Positive.
6	L. L.	13	Right upper	37,550	3	....	Recovered	Negative.
7	M. V.	35	Right lower and middle	11,700	9	Nephritis	Died	Positive.
8	N. W.	42	Right lower	16,500	8	....	Died	Positive.
9	E. D.	18	Left lower and right empyema	11,300	5	Empyema	Recovered	Negative.
10	J. S.	56	Left lower	11,800	1	....	Died	Positive.
11	G. C.	22	Left lower	36,000	6	Pleurisy	Recovered	Negative.
12	D. A.	32	Both lower	16,400	6	Pregnant (5 months) Nephritis	Died	Positive.
13	C. B.	26	Right lower	12,600	7	Pleurisy	Recovered	Negative.
14	A. D.	28	Both lower	15,100	5	....	Died	Positive.

Summary: Of the 14 cases, 8 complied with the rule, or 57.1 per cent.

As will be observed in the first group of 17 cases, 12, or 70.5 per cent., complied with the rule, while in the second group of 14 cases, 8, or 57.1 per cent., were positive, thus agreeing with the rule. Of the total of the two groups, 31 cases, 20, or 64.5 per cent., verified the observations of Gibson.

A reasonable explanation for four of the five discrepancies in the first group is to be found in the presence of a nephritis in three and a myocarditis and obesity in the fourth.

In the second group, of the 6 deviations from the rule, 3 were comparatively young, with soft elastic vessels, in which presumably a relatively lower pressure existed before the onset of the pneumonia, or, at least, were able to withstand a greater depression of the circulation.

Excluding the 7 cases in which a reasonable exception existed, of the remaining 24 only 4 failed to comply with the rule.

Aside from the prognostic significance, the blood-pressure and pulse ratio have been of the greatest assistance and satisfaction as a guide to the administration of cardiac stimulants. In some no stimulation was used, while in others one or two intravenous injections of digitalis were sufficient to reduce the pulse-rate, increase the blood-pressure, and produce a crossing of the curves.

REGENERATION OF BONE.[1]

By Franklin D. Smith, M.D.,
CHICAGO, ILLINOIS.

(From the Laboratory of Clinical Pathology of the University Hospital, Chicago, Illinois.)

The regeneration of bone, formerly with reference to the repair of fractures and in the past century to the ultimate fate of the bone transplant, has been a much-debated topic. One of the earliest and foremost investigators in this field of research was the French naturalist Duhamel du Monceau, who, in 1739, called attention to the active role played by the periosteum in the regeneration of bone. But the exhaustive work of the eminent French surgeon Dupuytren, placed the subject upon a scientific basis. Ollier, Barth, Axhausen, and others have presented many valuable contributions to the subject.

Cellular Dynamics. Some idea of cellular dynamics is essential for an adequate understanding of the physiological mechanism of transplanted tissue. The mere removal of a living cellular mass from its regulated supply of assimilative material—the constituents of the blood and lymph—does not mean death to its individual cells. Cellular life may proceed within certain limits without either organic or somatic influence and under proper chemicophysiological environment will retain its inherent vitality long after its enforced separation from living matter. Upon these fundamental physiological factors depend the eventual outcome of all transplanted tissue, bone included. The successful transplantation of tissue is dependent upon the continuance of the cellular life of the transplant, and likewise necessitates the growth of the individual elements or their regeneration. The living cell just before its removal from the donor is undergoing katabiotic and bioplastic activities respectively, dissipation of kinetic energy in the performance of function, and the conversion of kinetic energy into potential energy, *i. e.*, storing up energy in the formation of the complex molecules of the cells—substance growth. We can dismiss the katabiotic activity going on in the cell by merely stating, for lucidity, that these activities are the responses to external stimuli, either "directly or through the intermediation of the nervous system." The length of time the transplanted cell shall continue to functionate will depend upon the amount of potential energy that it carries with it. Highly differentiated cells will have reserved a minimum of potential energy, *i. e.*, the functional demand placed upon the bone cell is so great and hence its bioplastic activity so limited that even in the most favorable environment it (bone cell) could not be expected to regenerate sufficiently to maintain the unity of the graft. Therefore, since the vegetative potentiality of the bone cell is *nil*, the regeneration of the bone must come from a more embryonic cell. "The more we study the differentiated tissues of the body the more it is brought home to us that the fully developed and differentiated cell, as such, exhibits little active multiplication, and that to a very large extent, under normal conditions, the removal of the cell worn out by use is brought about by the presence and reproductive activity of 'mother cells,' of cells, that is, present in the tissues in a relatively undifferentiated form, or, as we are accustomed to term it, of embryonic type." (Adami.) The embryonic type of bone cell is the osteoblast which is everywhere present in true osseous tissue, in great numbers, in the compact periosseous layer, in the Haversian system, the marrow, and endosteal layer. In these cells, growth is at its maximum, function at a minimum; assimilation and growth with only slight functional demands are the distinctive features of their existence. The amount of reserved potential energy of any individual cell is extremely variable, but upon its reserve capacity depends the time limit of existence before new pabulum is supplied. With the establishment of a blood supply compatible with the demands of the graft, from a few hours to many days after the transplantation, the cells are in a more favorable condition for growth than when first transplanted. When existing upon their own reserve store of energy the cells gradually fall below the limit of maximum efficiency, so that as revascularization proceeds the cells are in active demand for new pabulum, stimulation to growth—or, as Weigert states it, "the katabiotic use of material in function removes the obstruction to growth." While the bone cells in the periphery of the graft have sufficient reserve force to maintain their vitality until reënforced by the permeation of the serum of the host, the bone cell encased in its calcified matrix at any distance from the new supply of food will become necrotic along with its ground substance. This calcium saturated ground substance must undergo dissolution before new bone can be laid down, and most likely the dissolved calcium salts are reprecipitated again by the rapidly maturing osteoblasts.

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[1] This article does not refer to the transplantation of compact bone into cancellous bone.

The graft consists of a multicellular mass, each cellular constituent composed of masses of biophores. The magnitude of growth of each unit mass of biophores is determined by two factors: (1) the relation of the area of surface contact of the unit mass of biophores to the intermediate substance (the cytoplasm), and (2) the relation of surface contact of the cytoplasmic mass to the surrounding assimilative material (plasma of the host). There exists a certain ratio between the optimum efficiency of the cells and their surface contact. Not until this maximum ratio is exceeded will there be nuclear division. It is readily conceived that the above relations vary for almost each individual cell of the transplant, since some cells will be more remote from the maximum supply of pabulum than others, and therefore changes in the biophores dominating the cells. Modification of the environment of like biophores, and eventually adaption of these biophores to this environment, constitutes the process of differentiation of the cells; differentiated osteoblasts are mature bone cells. Any gross change in the biophoric material is associated with corresponding alteration in the cytoplasm, histological and physiological modification of the entire cell.

Complexity of Bony Structure. The regeneration of bone is a very complex process. Bone is a tissue containing several important constituents, *i. e.*, the mature bone cell encased in a calcium salt deposit over which it rules; a complex Haversian system containing endothelium, fibroblasts, osteal fibroblasts in all stages of development, lymph spaces, and all the elements of circulating blood. Its matrix is a highly specialized ground substance which is capable of supersaturation with the earthy salts. Its many modes of development only serve to mystify the ultimate structure; probably no tissue in the human body has as many modes of development as bone. The complexity of the structure and development is the one obstacle encountered in the solution of any problem in which bone either alone or in combination with other tissues is involved. In the study of any problem or problems in which bone receives consideration, it is of paramount importance to keep in mind the presence of the osteoblast, which cannot be differentiated morphologically from the ordinary fibroblast, but which can assume the property of either secreting osseomucin or chondromucin, and eventually becoming, during its course of development, a highly differentiated bone cell, surrounded in its mature state by calcareous walls. By virtue of its inherent power, it is the ruler of calcium deposition within the area of its influence, and also retains the power of dispersing it. In the absence of any data, up to the present writing, to the contrary, the mature bone cell is an end-product, incapable of reproducing itself, and in the event of its death the calcareous ground substance, over which its ruling influence prevades, remains "inherently immutable," requiring time and foreign-body giant cells for its removal. Although it is possible to produce division by mitosis of the mature bone cell by incubating *in vitro* on artificial media, this must not be interpreted as being possible to produce new bone. Mitosis is not always synonymous with growth.

Development of Bone. In the consideration of the problems of regeneration of bone, it is advisable at this point to merely call attention to the many modes of regeneration and development of bone. In the embryonic state, it may arise either direct from fibrous tissue, in which case it is known as intramembranous bone, or it may develop from cartilage, as an intermediate stage, and is then known as intracartilaginous or endochondral bone. It is never of primary formation, although always derived from mesenchyme. Either method is complex in its development. After it has passed through the developmental stage and true bone is formed, the process of regeneration and repair are far from simple processes. In the repair of fractures, new bone may be formed direct or formed by passing through an intermediate stage of cartilage but eventually, however formed, fills in the space between the fragments. Loss in bony structure, however produced, may demand regeneration of bone for the preservation of the function of the part. This process will vary, depending upon the type of bone upon which such a demand is placed. The space may be filled in by bone formed from the periosteum or from osseous tissue *per se*. Either process will vary with membraniform bone or chondriform bone, while in the latter type of regeneration the cartilage cells may be (*a*) converted into bone cells and the surrounding matrix converted into osseous tissue, or (*b*) through the agency of fibroblasts, layers of young cells are deposited upon the cartilaginous remains. Just what role the marrow plays in the regeneration of bone is a much-disputed topic at present.

THE METAPLASTIC THEORY OF BONE FORMATION. True bone formation in vessel walls, etc.: In this connection, it may be well to pause and inquire into the mode of formation of true bone in heterotopic tissues, such as bloodvessels, the choroid coat of the eye, and in the ossification of laryngeal and tracheal cartilage in advancing age.

For many years the formation of bone in heterotopic tissues was considered a rare incidence. But since the work of Barth (1895), Pollack (1901), Sacerdotti and Frattin (1902), Poscharissky (1905), Bunting (1906), and Brueger and Oppenheim (1908), the formation of true bone, even with its associated cellular marrow (red), is not an uncommon occurrence. W. Harvey (1907), of Toronto, was able to produce true bone in the aorta of rabbits by the application of irritants to the vessel walls. In from two to six months after the application of a 3 per cent. solution of silver nitrate or a 2 per cent. solution of copper sulphate to the outer coat of the vessel wall of the aorta, Harvey was able to demonstrate the formation of bone with its Haversian canals, with bone marrow or bone alone, or the development of osteoid tissue in areas of calcification. A very important question naturally arises as to the mode of development of bone in these unnatural situations. The metastasis or displacement theory of Cohnheim assumes the presence, in these unexpected situations, of misplaced embryonic tissue, which by some unknown force takes on active vegetative development. This theory might be acceptable if it were not for the comparatively common occurrence of such.bony tissue, and moreover, the incidence points to a preponderance of such a frequency of occurrence of the process in advanced arteriosclerosis. Pollack found true bone formation adjacent to the calcium deposits in 43 out of 47 cases in which the process was studied. There are two views (Bunting) concerning the formation of bone in heterotopic tissues, *i. e.*, (*a*) that there is a direct metaplasia of connective tissue into bone after the manner of callus formation, and (*b*) that the calcific material is eroded with the formation of vascularized spaces containing tissue cells, some of which take on the function of the osteoblasts and lay down bone, some of the osteoblasts becoming included and forming the bone cell. Quoting from Bunting: "It seems clear, then, that one has here a metaplasia of connective-tissue cells into osteoblasts, for in vessels and heart valves there can be no possibility of periosteal or perichondral sprouts playing a part except in pulmonary foci. As to the stimulus which leads to this metaplasia there seems to be a uniformity of opinion, as might be expected, from the similarity of pictures presented by the different cases." Paul describes the process as consisting of three stages, as follows: (*a*) calcareous degeneration, (*b*) irritation about these areas of degeneration from fracture or other injury leading to inflammatory proliferation, (*c*) ossification in this young proliferating tissue.

Bone has always formed where young connective tissue is adjacent to calcium deposits and the metaplastic process is evidently a result of the chemical stimulus of the calcium salts. Bone cells, marrow cells, and connective-tissue cells are all developed from the undifferentiated mesoblastic cells, but in "adult life they seem to have diverged widely in nature and function." The specialized differentiation of a fibroblast into an osteoblast is a short step, and is dependent upon the nature of the intercellular substance deposited.

To return to the first appearance of true bone in the embryo, it is readily seen that highly differentiated osseous tissue is developed by a process of physiological metaplasia from the primary mesoblastic tissue, mesenchyme accompanied by a deposition of calcium salts. We must not forget that metaplasia is a constant process in the living body, occurring both as a physiological and pathological process, as is seen in the conversion of cartilage into bone and ordinary connective tissue into fat cells.

INDIRECT REGENERATION OF MATURE BONE CELLS. By the regeneration of any tissue is meant the reproduction of that tissue. The ultimate tissue may be produced in either one of two ways, *i. e.*, (*a*) through a process of direct regeneration (*e. g.*, epithelial cell from epithelial cell), or (*b*) by indirect regeneration (*e. g.*, erythrocytes from the mother-cell mononuclear of the marrow, etc.). A bone cell being an end-product cannot regenerate itself but must depend for its constant reproduction upon the indirect regeneration of the osteal fibroblasts with the ultimate formation of true bone cells. This process of indirect regeneration has been the stumbling-block of many researches in this field of experimentation. What is meant when regeneration of bone from bone is referred to? Certainly, regeneration of osseous tissue from osseous tissue does not refer to the reproduction of bone cells by mitosis with the formation of new bone cells and new ground substance with its deposited earthy salts. As far as the direct division of mature bone cells there is no available data, nor even a suggestion at the present time that such a division is possible in the human body. Therefore, any formation of new osseous tissue from osseous tissue must be by the indirect regeneration and development of its osteal fibroblasts into new-formed mature bone cells. Should a bone cell die through a deficiency of its inherent internal assimilation or a deficient supply of pabulum, as may happen in a transplant, the surrounding calcareous matrix over which the bone cell predominates does not undergo constant replacement and absorption, as any living tissue must, but remains unchangeable only to be removed in due course of time by the endothelial leukocytes, osteoclasts, etc. Therefore any new bone that is deposited, as in the case of the transplant, must be derived from the indirect regeneration of the osteal fibroblasts either of the transplant itself or from the host. This does not mean that all transplanted bone dies and that all new bone is laid down by the indirect regeneration of the osteal fibroblasts. Some bone cells are capable of retaining their inherent vitality and internal assimilation and reign supreme over their stipulated area of calcified matrix. However, it must be admitted, whether by analogy or by direct proof, that the entire quota of constituents of any transplant will not live, cannot live—while other constituents, more favorably situated, will be bathed with the necessary pabulum compatible with the retention of its inherent vitality.

Specificity of the Osteoblast. As to the specificity of the osteoblast, it will suffice to say that from the present animal experimentations its specificity is extremely doubtful. Should this view prove erroneous, then it must be considered as a wandering cell in the blood stream, which with our present histological technic cannot be identified as such. The theory of the metaplastic formation of bone, as in the walls of the bloodvessels, has much in its favor.

Bone a Living Tissue. Moreover, bone is a living tissue and not an end-product, as is generally considered. It undergoes both progressive and retrogressive metabolism throughout its life, exactly like any other tissue in the human body. Old bone is continuously resorbed and new bone laid down. Bone stores up calcium, to be drawn upon in time of need just as subcutaneous tissue stores up fat and the liver stores up glycogen.

Any tissue must undergo internal metabolic changes associated with constant renewal, absorption, and repair from the time of its inception as an entity until complete cessation of its activities. These properties seem comparatively simple when tissue, soft and cellular, undergoing direct regeneration, is under consideration, but when a tissue is apparently immutable because of its hard texture and its regeneration being dependent upon the indirect development of a mother cell the complexity of the process, at first sight, is immeasurable. The mechanical resistance of the hard, calcified matrix merely delays the process of interchange between its constituents and is only a matter of time, all processes of intercellular exchange taking place as in any cellular structure in the animated kingdom. Nails and wire used in the treatment of fractures, etc., produces localized absorption of the bone until the equalization of pressure is compatible with the vitality of the part. This process of absorption of bone under very limited pressure is seen in erosion of the ribs and sternum in an aneurysm of the aorta. Osseous tissue is very susceptible to perverted metabolic processes, as is seen in the pathological changes as a result of rickets, syphilis, tuberculosis, and osteomalacia.

Growth of Bone. It will be of some advantage, now, to consider the process or processes of the growth of bone both longitudinally and peripherally. Primarily, the growth of bone is dependent upon the internal secretion of both the pineal and thyroid glands, as is seen in cretinism, gigantism, and acromegaly. Disturbance in the secretion of the pituitary gland has been suggested as an important factor in the lamellar growth seen in osteitis deformans. McCord has definitely proved by feeding pineal gland to young animals, that in some manner it exerts a marked influence on developing bone. Feeding pituitary extract to fracture cases does not influence the time of permanent callous formation nor complete union of the fractured fragments, as has been shown experimentally.

The longitudinal growth of bone takes place at the metaphysis, *i. e.*, the diaphyseal side of the epiphyseal cartilage. In this situation, because of its nature and construction, the osteoblasts receive an abundance of pabulum for the continuance of their vegetative existence and also sufficient space for their proliferation, free from unnecessary crowding of the ultimate individual constituents. The growth of bone in this region is dependent upon the ossifying cartilage, which initiates the process and contains a full quota of all the elements necessary to its future development. If for any reason the cartilage at the epiphysis should undergo a destructive process with the complete elimination of this type of tissue, then epiphyseal proliferation would no longer be possible or at least would be retarded. Under normal conditions the growth of the bone is limited to the metaphysis; however, should the same conditions prevail in any portion of the diaphysis, the osteoblasts in this area would be stimulated to increased vegetative activity with their resultant specialized ground substance and the formation eventually of bone. These conditions are present when a limited length of the entire circumference of the shaft of a bone is removed. The gap will eventually be filled in by the proliferation of the osteoblasts in this region, both from the ends of the bones and from the periosseous layer of osteogenetic cells. Moreover, there will be renewed activity at the metaphysis with the formation of bone pushing the entire shaft toward the defect.

Bone is increased peripherally by subperiosteal osseous new formation, from the activity of the periosseous osteogenetic layer of the compact bone. This view is accepted by all during the period of development, but is contested during adult life.

Brief Résumé of the Literature. While it may seem a repetition of past publications to attempt even a brief *résumé* of the literature, since an attempt has been made to give due attention in a number of recent contributions on the subject, nevertheless the interpretation placed upon each set of experiments and conclusions varies both with the individual's fitness, either merely as a scientist or as a clinician, and with the subject matter under consideration. I shall attempt to limit my *résumé* of each investigator's researches to the statements and conclusions, specifically referring to the regeneration of bone *per se*. No attempt will be made to discuss pro or con the conclusions, but rather to allow each individual, unbiased, to formulate his own deductions.

Axhausen (1907–1909): "The chief source of new bone which replaces the necrotic bone of the transplant is the periosteum, then next in order comes the marrow and endosteum, and third, only in case of implantation into bone defects, the osteogenetic tissues of the implantation site."

Tomita (1908) concludes that new growth of bone comes from the inner layer of cells of the periosteum and from the marrow cells. The cells of the bone itself has no power to form new bone.

Wieder (1908): "In the regeneration of bone all the various elements, viz., periosteum, cortex, endosteum, and marrow, assist in the process." "Cortical bone-forming activity does not manifest itself until after considerable absorption of the cortex has occurred, so that it may be due to the liberation of bone cells which take on new activity and again precipitate the liberated calcium salts in new situations; or it may be due to the opportunity for the ingrowth of endosteum into the widened spaces." "The deeper layers of the periosteum, the endosteum, the tissues lining the Haversian canals, and the bone cells are probably all related or identical tissues exhibiting different activities, because existing under different physical conditions."

Baschkirzew and Petrow (1912): "There remains nothing else possible than to accept the view that the chief source of the regeneration of bone transplanted into soft parts lies in the primary layer of granulation tissue which surrounds the transplant. Bone in different degrees of necrosis seems to exert a specific irritation upon the connective tissue. Bone freed from the periosteum transplanted into soft parts proves themselves capable of regeneration; periosteum is as little necessary as the marrow."

Cotton and Loder (1913): "The essential picture is summarized as follows: Disappearance of the bone cells in the trabeculæ of the transplant and also to some distance in the host. The graft is covered by a layer of endosteal new bone which unites with the endosteal new bone of the host. New bone is formed by the activity of the endosteoblasts in all parts of the graft, centre and periphery."

Lewis (1914): "Cortical bone free from its periosteum, endosteum, and marrow will retain its vitality and proliferative power when subdivided into small fragments and replaced into the tissues. Contact with living bone is unnecessary for the growth of the transplant; larger pieces of bone may be transplanted and remain alive, not being merely grown into by the bone in which they come into contact." "Bone may unite after a fracture, or a space fill in after resection without the aid of any periosteal or bony bridge." "Contradictory results of careful observers can be explained by the variation in one factor, namely, the amount of blood supply which the transplanted bone obtains."

Bancroft (1914), in discussing the process of repair of bone following trauma, states that "one is impressed with the idea that the calcium salts have been laid down upon ordinary granulation tissue in the perivascular spaces; that is, in the area farthest away from the bloodvessels. This is early formation of new bone."

Mayer and Wehner (1914) state " that under favoring conditions many bone cells of the transplant can maintain their vitality until the transplant has become vascularized. The cells of the Haversian canals, particularly of the young bone, possess osteogenetic power provided their vitality is maintained. A greater part of the transplant necrosis, and that these necrotic areas are gradually replaced by new bone derived from the specific osteogenetic cells of the periosteum, endosteum, and Haversian canals. In bone transplants the bone cells showed no new formation of bone. A part of the transplanted bone dies, another part lives until the transplant is vascularized. The dead bone is partly dissolved by the young bone cells, which form new bone at the same time, which is gradually substituted for the old bone and penetrates into the old bone cavities."

Gallie (1914): "Death of the bone graft by the end of the first week. Revascularization of the graft by the second week. That in bone grafts as well as in living bone, bone absorption and bone building are the properties of living bone cells. By the end of the third week the graft is completely covered by new bone."

McWilliams (1914): "Living bone grafts have life inherent in themselves and are capable of permanent growth even when transplanted into soft parts."

Phemister (1914): "Osteogenesis in bone repair occurs from the inner layer of the periosteum, from the endosteum, and to a much less extent from the bone cells and fibrous content of the Haversian canals. The great mass of bone cells being away from the surface and surrounded by an extensive and difficulty permeable calcified matrix gradually undergo necrosis and absorption. A few (bone cells) about the periphery and lining the larger vascular spaces as well as the fibrous elements of the latter may survive and proliferate. A fracture through a transplant unites by callus formed from the surviving cells of the transplant in the vicinity of the fracture."

Macewen (1912): "The vegetative capacity of the bone cell is at least as great as that of the epithelial cell. Diaphyseal bone graft lives and actively proliferates in its new surroundings. That diaphyseal bone is produced by the proliferation of the osteoblasts derived from the preëxisting osseous tissue. As long as the bone cell remains embryonic, it exhibits the power of proliferation; when it reaches maturity it assumes the fixed tissue type and becomes stationary. This period is coincident with the calcareous deposition, and with it the cessation of active regeneration, though its proliferating potentiality still remains. The regeneration of bone is proportionately in inverse ratio to the size of the graft. The vegetative capacity of the bone cell is as great as that of the graft. The vegetative capacity of the bone cell is as great as that of the epithelial cell, and if one grants not only the vitality of the transplanted epithelium, but also its power of extensive proliferation, then, judging by analogy, the bone cell ought to show equal capability of living and growing when transplanted."

That practically all the bone cells of the transplant necrose is supported by Barth, Bonome, Marchand, Saltykow, Axhausen, Frangenheim, Baschkirzew, and Petrow, while the theory that the graft retains its vitality and proliferates is supported by Macewen and McWilliams. Phemister is inclined toward the former view, but states that the bone cells about the periphery of the graft may survive and proliferate. No doubt the process involved is as complicated as the structure is complex, and no one theory will explain the changes in detail.

Method of Study. The studies of the regeneration of bone in this article are based upon the histopathological changes produced at varying periods of time after the operative procedures. The operative procedures were confined entirely to the practical application of the transplant, such as medullary transplantation, either cortex of the crest of the tibia or fibula complete, excluding macroscopic evidence of the periosteum; inlay transplantation, using an osteoplastid containing a full quota of elements, periosteum, endosteum, and compact bone, placed in apposition to its corresponding layers of the host. All experiments were performed on dogs, rabbits, or sheep, constantly employing the isoplastic or homoplastic methods. While these methods of experimentation are not entirely satisfactory, due to the dual process of repair going on simultaneously, *i. e.*, repair of fracture and regeneration of the transplant, nevertheless the exact duplication of the practical application of the problems and the complexity of the structure under consideration is so great that each individual element cannot be studied separately, the method outlined above is not without its favorable points. Many experimenters have endeavored to separate the various constituents of bone by removing periosteum and transplanting each singly to determine its bone-forming capacity. These have been only futile attempts, as it has been shown elsewhere that it is impossible to remove the periosseous layer of osteogenetic cells with the periosteum without at the same time removing a considerable portion of the cortex. Any attempt that has been made has been a recourse to false security and is unscientific.

Four Factors Involved in the Successful Transplantation of Bone. When an osseous transplant is transplanted into bone, either to fill in a loss of substance or to lend mechanical support to the ends of a fractured bone, there are certain chemical, physical, and physiological demands placed upon the transplant itself, and also upon the adjacent tissues of the host, namely:

1. Temporary maintenance of nutrition not lower than the minimum compatible with the retention of the complete internal assimilation of the various elements of the transplant.
2. Permanent establishment of a sufficient pabulum for the transplant, by the revascularization of the Haversian system of the transplant from the necessary constituents both of the host and the transplant.
3. Complete osseous union between the transplant and the host.
4. Eventual metamorphosis of the transplant into an osseous entity complete in its contiguity with the adjacent tissues of the host.

LAW OF FUNCTIONAL ADAPTATION. Bone transplanted into bone, for specific and physiological reasons, subjected to varying stress and strain, will eventually be governed by the same laws as any other tissues under similar physiological demands. Normal tissues react both to their environment and functional requirements, as pointed out by Wilhelm Roux and known as the law of functional adaptation. This law may be stated as follows: The relation of the conformation, size, and architectural structure of any tissue or organ is dependent upon the functional demands placed upon that tissue; also, any variation in either of these demands will produce histological changes in the tissues sufficient to meet these variations. Transplanted tissues are not exempt from these conditions, and bone transplanted into a defect in bone, to supply a physiological demand and to perform specific functions, will undergo specific changes in its structure commensurate with these demands, *i. e.*, those bone cells retaining a sufficient reserve force to overcome the temporary enforced decrease in pabulum will eventually hypertrophy, subsequently take the place of necrotic bone, and finally functionate in their new locality. This hypertrophy of transplanted bone is well shown in those cases where a complete fibular graft is transplanted into the defect in the tibia. In a remarkably short time the fibula will increase in diameter by the circumferential deposition of new lamellæ. The hypertrophy may be either local or general, and is dependent upon the local application of increased strain upon certain portions of the graft, as in the case of muscle pull or stress applied over its entire structure. Certain functional demands upon the graft are necessary for its future welfare, for in those transplants where there is neither physiological nor mechanical function to perform, while the cells will retain their vitality, their proliferative activity will be materially decreased. Transplanted tissues upon which no functional demands are made will gradually diminish in size, as clearly demonstrated by Lewis and Davis in transplanted tendons, and also by Halsted, who demonstrated that parathyroid tissue would undergo absorption unless a partial parathyropriva primarily existed. No doubt these conditions account for the absorption of the osteoplastid transplanted into certain muscles. Lack of functional demands causes atrophy and absorption.

Because of the tendency to use terms involved more or less loosely, an attempt will be made to limit their application to certain specific entities: Does the term bone cell refer only to the mature cell encased in its calcified matrix? If it is employed in such a sense, then we cannot refer to its vegetative capacity. The term should be applied only to the end stage of development of the osteoblast, encased in its calcified matrix, and in this sense it retains its inherent vitality; but as to its "vegetative potentiality," it is very doubtful. It will not be employed as a collective term, including the osteal fibroblast and its subsequent developmental stages. The osteoblast is a derivative of the undifferentiated osteal fibroblast, and represents a stage of differentiation between the fibroblast of the periosteum, endosteum, and Haversian system and the mature bone cell.

THE FATE OF THE BONE TRANSPLANTED DURING INFECTION. The behavior of the transplant in the presence of an infection will be given special attention. The changes brought about in the transplant as a result of an infection will depend (1) primarily upon the virulence of the infecting microörganism, and (2) upon the different elements which constitute the osteoplastid, viz., the presence or absence of the periosteum will materially influence the extension of the infecting agent while the location of the infecting organism may account for non-union or even fracture of the transplant. Moreover, an infection of the marrow substance of a fibula transplant will add a serious complication, necessitating a second operation and detraction from satisfactory end results.

In the case of a fibula transplant there are three distinct sites of infection, *i. e.*, the marrow and either end of the transplant. A mild infection may be taken care of by the serum of the host if occurring at either end of the transplant. The process of repair at either end would be considerably delayed, depending upon the recognition of a suppurative osteomyelitis and the establishment of sufficient drainage. A properly fitting fibula transplant immediately restores the continuity of the bone, and in case of infection also seals up the active microörganism, which may demand drainage in the future. In the presence of an infection of more or less virulence the transplanted tissue, within its sphere of toxic influence, will undergo necrosis. Infection in a tibia (crest) transplant if suppurative will eventually establish a sinus sufficiently large to take care of the necessary drainage. At the line of fracture the process may become localized, and by necrosis and absorption of the transplant in this region may become so weakened as to fracture at this site.

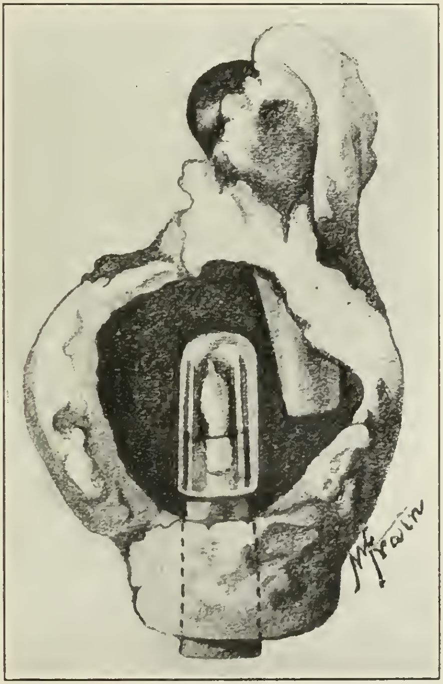
Infection of the transplant with an established sinus does not effect the eventual formation of the external callus, but rather acts as a stimulus to osteogenesis, and an excessive callus is laid down with the immobilization of the fragments. However, an infected transplant will demand removal, since bone dissolution and absorption is very slow, taking months to remove a small transplant.

As the process of infection in other types of transplants, *i.e.*, transplants with the periosteum intact, quoting from Phemister, "these structures (periosteum and medullary substance) may survive and have a reëstablishment of circulation despite the mild infection. The surviving periosteum forms a new layer of bone about the cortex, which both in its excessive amount and in its coarse, spongy character resembles the involurum surrounding the involved shaft in osteomyelitis." "Absorptive changes in the dead cortex are very much accelerated. The surface is eroded, the Haversian canals are dilated, and since deposition of new bone does not keep pace with bone absorption the cortex is rendered somewhat porous in structure."

GLASS-TUBE EXPERIMENT. The humerus of an adult rabbit was cut in two near the condyles and a compact isobone graft was transplanted into the medullary cavity of the distal end, allowing about 2 cm. to project out. Over this free portion cf the osteoplastid was placed a glass tube which was sealed at one end and the other end was driven over the distal end of the humerus. The internal diameter of the tube about the transplant was about three times the diameter of the graft. This portion of the tube immediately filled with blood clot, completely surrounding the graft with nutrient plasma. Muscles and hide were sutured with silk. After six weeks the rabbit was bled and the transplant was examined. There was slight proliferation of the osseous tissue about the sawed end of the humerus and also necrosis and absorption about the circumference of humerus from the tight-fitting glass tube. The graft immediately adjacent to the end of the humerus had not increased in diameter, but the free end of the transplant had increased to at least twice its former diameter by circumferential deposition of new bone. While most of the mature bone cells had disappeared, there was evidence of active proliferation of the osteoblasts, especially about the circumference of the distal portion of the transplant.

If transplanted bone (non-infected) is undergoing a process of continuous absorption, as is claimed by some observers, why do we not find more frequently the endothelial leukocyte and the foreign body giant cell—the osteoclasts of Kölliker—for bone absorption cannot proceed by any other process? Osteoclasts in the majority of microscopic sections of transplanted bone must be searched for, and are not nearly as common as the literature would lead us to believe. While it must be admitted that even isobone will undergo absorption in some animals, just as heterobone is absorbed in the majority of untreated animals, nevertheless, it is only the occasional animal in which the isobone transplant is absorbed, and far from the majority. Even heterobone has been known to remain in the human body for years (sheep to man, Drew) and perform its function.

In some cases the absorption of the isobone has been known to be dependent upon the treatment of the osteoplastid. The bed for the transplant must by all means be prepared first and the osteoplastid removed and transplanted immediately, and with very limited manipulation. Small grafts placed in bichloride of mercury (1 to 50,000) for three minutes were always absorbed, likewise grafts were absorbed when the hands were carelessly washed in bichloride (1 to 2000) and rinsed in sterile water. This procedure was at times accompanied by signs of necrosis about the prepared bed. Alcohol (1 to 20,000) for five minutes is extremely injurious to the graft, and its use was always associated with absorption. Freezing, while it has been successful with some tissues, has been unsuccessful in this series of experiments. Heat (110° F.) has been extremely injurious, and has been the source



Transplant in glass tube, six weeks after transplantation.

of considerable trouble in the human transplantation of bone. It is not out of the ordinary to record a temperature of 160° F. taken from the saw immediately after going through three inches of cortex and exercising considerable care. If it is necessary to depend upon the bone cell in the periphery of the graft for its future maintenence, as there are sufficient indications at present to substantiate this view, then it is of paramount importance not to allow the saw to become heated. A few other antiseptic solutions, such as are found in the armamentarium of any well-equipped operating room—mercury cyanide, formaldehyde, etc.—were experimented with. The results were about equal to those cited above.

THE FATE OF THE MEDULLARY ISOBONE TRANSPLANT.[2] *Early Absorption of the Transplant.* Absorption of neither isobone nor heterobone is due to "changed serological relations," as has been claimed by certain observers, since as it has been clearly shown by Lambert and Hanes that transplants are capable of maintaining their vitality, *in vitro,* under artificial incubation, in heteroplasma of a limited variety of species, from which one readily concludes that absorption is not due to a lack of proper food material but rather to some inherent capacity of the cellular elements of the blood or surrounding tissue. Whatever inherent power produces such biochemical differences as to promote autolysis and absorption of the isoplastid, it is certain that the process differs from that which produces absorption of the heteroplastic, the former being dependent upon the bloodvessels and stroma (Bashford) while the latter is dependent upon an immunization process and the action of the macrocytes.

The absorption of the isoplastid, due to sensitization by foreign proteids (production of specific (?) ferments), is one factor which will occasionally account for the disappearance of the graft in a very short time, although in such a delicate process as the transplantation of living tissue, absorption may be brought about by many other factors.

More mature bone cells in the periphery of a graft will retain their vitality than in its central portion. Therefore, more bone cells will retain their vitality per unit of mass of transplant in a complete fibular transplant with two surfaces of the compact bone in contact with the plasma of the host than could be expected in a tibial (crest) transplant with only its external surface in contact with the surrounding plasma. Correspondingly more of the calcium saturated matrix will remain intact, since it is directly under the influence of the mature encased bone cells. The fibulaplastid will require less absorption and replacement than a tibiaplastid, and therefore the surrounding tissue reaction will cease earlier, viz., shorter convalescence.

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[2] These remarks apply only to a periosteal-free compact bone transplant placed in the diaphysis and do not refer to bone transplanted in cancellous tissue in proximity of the epiphysis.

Early Changes Immediately Adjacent to the Transplant. The space between the bone of the host and the osteoplastid where it is not in direct apposition will immediately become filled with coagulated blood and lymph. The clot in time will undergo organization, with the formation of osteoid tissue through which new capillaries will push themselves to the osteoplastid and form a network of fine anastomosing capillaries around its surface. From this vascular network small capillaries are seen to enter the empty Haversian canals.

At either end of the graft a blood clot will be formed, the size of which will depend upon the traumatism to the marrow substance. If the marrow substance has been injured by forcing the transplant against it, producing undue pressure, the changes at the end of the bone are delayed until the proper equalization of pressure is produced by necrosis and absorption. If the marrow has been removed for a sufficient distance, so that the osteoplastid does not produce pressure atrophy and necrosis of the marrow, then both ends of the transplant will be sealed off from the remaining marrow cavity by a blood clot. This occurs within the first twenty-four hours. The endosteum, which has been previously removed from the medullary cavity by curetting, proliferates, covering over denuded bone as far as the blood clot, and later will gradually extend across the concave surface of the clot, sealing off the proximal and distal medullary cavities from the graft by a limiting layer of endosteal cells.

The blood clot at either end of the graft extends farther up on the side of the medullary cavity than it does in the centre, forming a concave surface on the clot.

The blood clot gradually undergoes transformation into osteoid tissue, and in the case of the fibula transplant the osteoid material forms a plug extending into the medullary cavity of the fibula. The transformation of the clot into osteoid material takes place much more quickly than at the sides of the graft, *i. e.*, between it and the host. The calcification of the clot at the ends of the graft progresses quite rapidly, so at the end of thirty days both ends of the graft are solid in the marrow cavity.

The space between the ends of the fractured fragments become filled with clot which finally organizes, but for some unknown reason does not undergo calcification and ossification until many months later. (Approximately seven to nine months in the tibia of a dog, and if conditions are not favorable, this time is materially increased.) This delayed process of calcification is probably due to atrophy of the ends of the fractured fragments extending back from the ends to a varying distance. Not until regeneration has been completed in these atrophied ends does the cicatrix between the fragments undergo calcification and ossification.

This same process of delayed calcification takes place within the medullary cavity, and is especially marked when the transplant is not rounded to fit the medullary cavity. In this the edges of the graft under pressure undergoes necrosis and absorption by the osteoclasts until the pressure is equalized and compatible with the vitality of the surrounding living tissue. While the primary purpose of the medullary transplant is to immobilize the fragments, nevertheless any undue pressure between the transplant and the compact bone of the host will produce a delay in osseous union.

These processes of necrosis and absorption are retrogressive, and are not compatible with regenerative and reparative processes. Not until these retrogressive processes have completely subsided is it possible for any process of a reparative nature to take place. This simply means a delay in a process which is of primary importance, being secondary to immobilization and the proper coaptation of the fragments. Moreover the process of absorption is dependent upon the physical condition of the patient, and is commensurable with the variability of any such process in the human body. The end products of pressure necrosis and degeneration are conducive to excessive callous formation, and consequently detrimental to the complete restoration of function when the fracture is in proximity to a joint, causing limitation of motion.

Any tissue, such as muscle, fat, marrow (?), periosteum, endosteum, etc., which may find lodgement between the compact bone of the host and the transplant will produce a cicatrix which will not become calcified, producing merely a fibrous tissue union.

Finally the conformation of the new osseous development is dependent upon the balanced action of the formative osteoblasts and other cells, osteoclasts which remove any excess of spicules of bony development and mould the bone.

Some of the Haversian canals of the graft become filled with coagulated blood, which will cause necrosis and absorption of the osseous tissue of the area which the canal had supplied. These portions of the Haversian canals do not undergo revascularization, but are eventually replaced by the method of "creeping replacement."

Deposition of calcium in osteoid material at the ends of the transplant must not be mistaken on the interpretation of roentgenograms for absorption of the graft, since serial roentgenograms at weekly intervals demonstrate this area of lessened intensity to be progressive and not retrogressive, as must necessarily be the case in peripheral absorption. Invariably at the end of six months the medullary graft has increased in length and the spindle-shaped ends are due to progressive deposition of calcium in the osteoid material, which is deposited soon after the insertion of the osteoplastid.

Death of the Bone Cells. During the normal metabolic activity of osseous tissue the matured bone cell is constantly being replaced by osteoblasts which have reached the stage of complete maturation. Whether the lacunar space occupied by the wornout bone cell is to be occupied by the new bone cell is not known, although after taking into consideration the complicated structure of the bone cell with its ramifying fibrils extending through the canaliculi it does not seem feasible that such a process of replacement were possible. All the stages of maturation are present at one time during the normal economy of osseous tissue metabolism from the fibroblast to the fully differentiated bone cell. If this is the case in normal bone development we should at least be prepared to accept the same conditions for transplanted bone. In the osteoplastid we find bone cells in all stages of destruction, which continue at a greater rate than in normal osseous tissue. From the second to the tenth day there appears no limit to their destruction. However in each cross-section many living bone cells are always found in the periphery of the graft, while in the central portion the majority will be found shrunken and dead. Many lacunæ are completely devoid of any cellular life, and the staining reaction of the calcified material in its neighborhood is the best guide for the interpretation of the death of the bone cell. Empty lacunæ do not necessarily mean dead bone cells, especially not with our present histological technic. Furthermore it must be remembered that a few bone cells in the host after curetting the endosteum will die, as already shown by Cotton and Loder. Occasionally after a bone cell has taken up its task of producing new bone in the transplant, as shown by the deposition of a few lamellæ of bone, the cell will be found shrunken and the staining reaction deficient. Evidently the bone cell did not have the necessary reserve force to hold out under such a difficult environment. The process of calcium deposition will immediately be assumed by another bone cell. The metabolic interchange in a transplant must necessarily be many times greater than normal to keep up with the increased tissue destruction and absorption.

Reëstablishment of a Permanent Circulation. In normal bone the Haversian canals contain several types of tissues, *i. e.*, the small artery, a large vein, a very narrow lymph channel, and cellular tissue. In the transplant all of these structures are seldom seen. Lymph vessels and veins have not been observed at any age of the transplant. The fine capillary network surrounding the graft, as described above, send fine capillaries into the substance of the transplant wherever it is possible to gain an entrance. No preference is given to the Haversian canals. Occasionally a small capillary has entered the graft only a few microns to the side of the Haversian canal, and shows no indication of preference for the canal. In the fibula transplant the capillaries pass through the compact bone and ramify with the capillaries of the marrow substance. As a rule, most of the Haversian canals show new-formed capillaries, but some are filled up with a coagulated, structureless substance with no indications of bloodvessels.

In constant association with the new-formed capillaries are seen numerous large cells which vary in morphology, and are no doubt maturing bone cells. They are situated on the outside of the vessel wall; sometimes, especially in large Haversian canals, they are in no relation to the bloodvessels, with the exception that they are invariably present. Occasionally these cells have been seen to occupy recesses in the calcified matrix at the side of a small capillary.

The reëstablishment of the permanent circulation is one of the most important stages in the life of the transplant, since not even a beginning of capillary proliferation has been observed in those heteroplastic transplants which sometimes are so readily absorbed. This same process has been seen in heteroplastic transplants taken from the most varied species (pigeon to rat), although a large percentage shows no evidence of capillary proliferation at all.

In the fibula transplant the capillary circulation throughout its marrow substance is readily established, aiding in an early supply of pabulum to the compact bone.

Methods of New Bone Deposition. In any transplanted bone considerable new bone must be laid down to insure the continuity of the graft. In the normal living bone this new bone is almost entirely supplied by lacunar deposition. In transplanted bone, while Axhausen maintains that lacunar absorption and subsequent bone apposition are sufficient to explain the replacement of all new bone, nevertheless, replacement of osseous tissue by direct contiguity—so-called "creeping replacement" (Schleichender Ersatz)—is frequently observed. Bone absorption and bone building are properties of developing and mature bone cells. Bone is absorbed with the liberation of carbonic acid (Hofmeister) setting free the earthy salts for the synthesis of the new bone by the mature bone cells.

The necrotic bone becomes absorbed under the influence of the mature bone cells and new bone is deposited, layer after layer, by these same cells. This process is constantly being observed in all sections of transplanted bone. Occasionally the necrotic bone is replaced by tissue laid down in its immediate vicinity by young bone cells which produce changes in this dead bone by the fibrils which penetrate its substance, and in this way gradually exert sufficient influence over it to produce absorption and deposition of new bone.

Metamorphosis of the Entire Osteoplastid into a Complete Osseous Entity. With the complete reëstablishment of the circulation and deposition of new bone for the necrotic calcium saturated matrix the osteoplastid becomes, after many months, an osseous entity directly continuous with the adjacent osseous tissue of the host. All osseous transplants will not progress to this same degree, since some transplants stimulate osteogenesis to a greater extent than others, producing a large callus sufficient to supply the necessary mechanical demands placed upon it. In such a case the osteoplastic would no longer be required, and its metamorphosis may be discontinued at any stage of the transformation. The time necessary for the complete metamorphosis of the osteoplastid depends upon the size of the graft, condition, and age of the host, and will vary from one to two years.

Final Absorption of the Transplant. The transplant is not a permanent entity, since a gradual decrease in the functional demands is associated eventually with the complete absorption of the graft. This is shown very early in transplants placed in the medullary cavity of the humerus[3] for the repair of recent fractures. In this location in a healthy individual all mechanical demands are removed early with a corresponding early absorption of the osteoplastid. In one case[4] after an excellent result the transplant is undergoing absorption as early as the fourteenth month after operation. Complete absorption will take place in from two to five years, depending upon the size of the graft, age of the patient, and the place of its insertion.

CONCLUSIONS. 1. Osteogenesis is not a specific attribute of any tissue or layer of cells, but is limited entirely to the osteoblasts which are scattered throughout the entire structure of the osteoplastid and the host.

2. Mature bone cells are end products, and while they may undergo mitosis under artificial conditions, this proccess is unknown in the human economy.

3. Many mature bone cells of a transplant remain alive, especially near the periphery of the transplant, and control its surrounding calcified matrix.

4. Absorption of isobone is influenced in many cases by the treatment received by the transplant.

5. Protoplasmic poisons should not be employed during bone-grafting procedures.

6. Regeneration of bone for the most part is an indirect process through the differentiation of the osteoblast to a mature bone cell.

7. A transplant is subject to the varying demands of its environment; functional demands producing an increase in bone deposition; lack of functional demands causes atrophy and absorption.

8. Bony contact is not essential to regeneration of bone, but for practical purposes, doubly insures the result desired.

9. In the transplantation of any bone, the most that can be hoped for is the continued development of the implanted osteoblasts,

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[3] Absorption is not the rule when an entire humerus is replaced by a complete fibula transplant, as in case of sarcoma of the humerus.

[4] Case to be reported by Dr. Charles Davison.

together with such stimulus as may be obtained from the osteoblasts of the host and the retention of vitality in some of the transplanted bone cells with their corresponding intercellular calcium matrix.

10. The transplant in the presence of an infection may or may not survive, and is dependent upon the type of the infecting agent.

11. The medullary transplant is not a permanent entity, but is absorbed as soon as all functional demands are removed.

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REVIEWS

Pulmonary Tuberculosis. By Maurice Fishberg, M.D., Clinical Professor of Tuberculosis, New York University and Bellevue Hospital Medical College; Attending Physician, Montefiore Home and Hospital for Chronic Diseases, New York. Pp. 639; 91 engravings and 18 plates. Philadelphia and New York: Lea & Febiger, 1916.

In the author's words, "It is the purpose of this book to supply the general practitioner with information concerning the etiology, diagnosis, prognosis, and treatment of pulmonary tuberculosis, its clinical forms and common complications." He has had an experience of eighteen years with tuberculosis problems in New York City to fit him for the task. Great pains have been taken to present the many varied subjects in a broad way, and at the same time to keep them within proper limits. The constant evidences of the author's own experiences, and his frequently expressed personal opinions, stamp the book with distinct individuality. Good sense and judgment are frequently displayed, for example, in advising physicians to tell their patients when they are suffering from tuberculosis, and in warning the general practitioner against using tuberculin in treatment. The author's wide reading, and the many references furnished, add greatly to the value of the volume. Among the good features of the work are the emphasis laid on the great importance of the home as a factor in the problem of tuberculosis, especially in regard to treatment, the importance attached to the constitutional symptoms in deciding whether a person is ill from tuberculosis, the importance of tuberculosis in the aged, and the importance of economic conditions as affecting the diminution of tuberculosis. Under physical diagnosis it is a pleasure to see the amount of attention given to inspection. The treatment of pulmonary tuberculosis is based on personal experience and considerable reading, and many of the requirements for handling this important subject have been fulfilled. The illustrations and index are a great help to the volume.

On some subjects more could have been said with advantage, for example, about differential diagnosis, about anesthesia in operations on tubercular patients, and about the treatment of tuberculosis complicated with pregnancy. The subject of vocal fremitus receives very little attention. It would have been profitable to discuss the value to medical men, both students and physicians, of clinical instruction in tuberculosis.

The author is profoundly impressed by the evidence favoring the theory that the adult human being is in very slight danger from exposure to tubercle bacilli outside himself, because of a supposed immunity developed in childhood, and his belief in this theory has greatly colored his practical suggestions in regard to prophylaxis. It is to be feared that some who read this book may fail to sufficiently realize the great importance of the prevention of tuberculosis, about which too much care cannot be observed along a good many different lines, at least so long as a great number of problems regarding the dissemination of this disease remain only imperfectly solved.

There are a variety of opinions and statements in the book that are liable to adverse criticism. Thus it is stated, in speaking of auscultation of normal persons, that "there are many individuals in whom bronchial breathing is heard all over the upper parts of the thorax" (p. 282). In another place it is asserted that "rales are only produced when the caseous material softens and breaks through the wall of a bronchus" (p. 283). Profuse hemorrhages are said to be seen only in advanced consumptives (p. 199). According to the author, active phthisis is extremely rare in cases of heart disease (p. 196). The administration of the iodides is given as one of the methods for obtaining expectoration in early cases (p. 159). In some respects the directions given about exercise are too liberal (p. 476). I do not consider nasal breathing on the part of the patient during auscultation of the chest, as recommended by the author, to be as generally available as oral breathing. The propriety of submitting another classification of cases of pulmonary tuberculosis is open to question.

While unable to agree with the author on all points, the reviewer has derived much pleasure and profit from a perusal of these pages. The book is informing and is calculated to stimulate one's interest in many of the puzzling problems associated with pulmonary tuberculosis. C. M. M.

ELEMENTARY BACTERIOLOGY AND PROTOZOÖLOGY. FOR THE USE OF NURSES. By HERBERT FOX, M.D., Director of the William Pepper Laboratory of Clinical Medicine in the University of Pennsylvania. Second edition, revised and enlarged. Pp. 251; 68 engravings and 5 colored plates. Philadelphia and New York: Lea & Febiger, 1916.

THE scope of the book is indicated in its table of contents, which follows: Chapter I, introduction, history, place of microörganisms in nature; II, morphology, reproduction, chemical and physical properties; III, general biology, including the chemical changes wrought by bacteria; IV, methods of study, sterilization by heat; V, destruction of bacteria by chemicals and their practical use; VI, relation to disease, immunity; VII, preparations for and procuring of specimens for bacteriological examination; VIII, the acute chiefly localized infections of pus nature, the pyogenic cocci; IX, the acute self-limited infections; X, the more chronic infectious diseases; XI, various pathogenic bacteria not associated with a specific clinical disease; XII, yeasts and moulds; XIII, bacteria in air, soil, water, and milk; XIV, diseases due to protozoa; XV, diseases of unknown etiology; glossary.

The reviewer can criticise but little adversely. On the other hand there are several features that stand out most prominently and favorably because they are unusual in a text-book for nurses: First and foremost the numerous and good illustrations. Second, descriptions of apparatus which the well-trained nurse may bring to the physician by naming (instead of description), as well as minor technical procedures. Again, the completeness of the book makes it perhaps a possible one for medical students, and certainly for that daily increasing body of laymen and women who occupy permanent and full-time positions in hospitals and other laboratories in technical capacities. F. D. W.

Diseases of the Stomach and Upper Alimentary Tract. By Anthony Bassler, M.D., Professor of Clinical Medicine, New York Polyclinic Medical School. Third edition. Philadelphia: F. A. Davis Company, 1916.

The third edition of Dr. Bassler's book is from the press and the work is too well known to merit any extended summary. The edition is amplified by a more extensive contribution to Roentgen-ray diagnosis and the inclusion of a number of half-tone plates which considerably enhance the value of the book. Diseases of the mouth, esophagus, and stomach are discussed in different chapters, and the whole is compiled in a thoroughly readable volume which has already had the approbation of the medical public. The chapter on laboratory diagnosis is satisfactory, and the chapter on feces is one of the best which has appeared in a work of this nature.

After discussing the anatomy, physiology, and chemistry of the stomach, chapters are devoted to the various laboratory procedures, clinical examination, therapeutics, medicinal treatment, physical methods of treatment, surgical indications, and finally the various organic and functional conditions of the upper alimentary tract.

The work is simply a revision of the former volumes and presents the subject in much the same way. It is, however, more decidedly clinical than scientific and from the stand-point of the practising physician more readily assimilated. From a critical stand-point, however, fault can be found with the work in that it is written too much from the stand-point of the gastro-enterologist *per se*, rather than from the logical view-point of gastrology as merely one of the highly specialized departments of internal medicine. Not enough insistence is placed upon the fact that many abdominal conditions are other than stomach and bowel, and in the opinion of the reviewer no work on diseases of the stomach is complete unless it presents in a cursory way gall-bladder, pancreatic, and ductless gland syndromes whose chief symptoms frequently masquerade in the region of the epigastrium. Furthermore, the definite tendency of internal medicine to become essentially analytical has not been sufficiently emphasized. We are slowly getting away from dyspepsia and chronic gastritis and reaching causes and effects.

Autonomic imbalance, and the whole question of sympathicotonia and vagotonia is merely skimmed over; aërophagia is not discussed in the light of recent knowledge; the newer secretory and motor investigations have been entirely overlooked. Such statements occur as "the gastric juice is not secreted in its normal state excepting during the process of digestion in the stomach," is at variance with recent discoveries. Frequently statements are confusing, such as, for instance, p. 36, "The first morsels of a meal take a general course anywhere in the organ, until a certain quantity of food is contained in the viscus, although Roentgen-ray observations with a fluid bismuth mixture show that foods drop directly downward from the cardia to a vertical point at the greater curvature and then flatten out there before they coat the inside of the organ," a statement which any radiographer will contradict, especially since long ago it was pointed out by Leven, Barret, Holzknecht and others, that even as little as 30 c.c. of liquid was sufficient to fill the so-called normal empty stomach, owing to its peristole function, and any real tendency toward flattening out is suggestive of atony.

We would suggest that Sippey's method be considered in the treatment of ulcer, that reference be made to the Haudek "nischen" symptom in penetrating ulcer. The tests for neoplasm, such as the protein concentration, formol index, antitryptic serum reactions, while none of them specific, might be included, as anything which will throw light on the possibility of this lesion should be emphasized. There is, furthermore, in this work, no consideration of gastric volvulus, subdiaphragmatic hernia, and the by no means rare achlorhydria hemorrhagica gastrica of Pilcher, which should be discussed in a work of this nature.

Apart from these points, which should be included and the references which are somewhat out of date, the book is to be recommended as a safe and sane exposition of diseases of the upper gastro-intestinal tract. Dr. Bassler is to be commended for the stand he takes on gastroplication and gastropexy as being unwarrantable surgical procedures, as well as the recommendation that the woman who is predisposed to ptosis should wear a satisfactory binder after labor, a point which many physicians entirely overlook. The book is full of much practical information, which cannot fail to be of value to the practising physician. M. E. R.

TASCHENBUCH DES FELDÄRZTES. II Teil. Herausgegeben von Generalärzt Professor Dr. Ad. DIEUDONNÉ, Geheimrat Professor Dr. M. v. GRUBER, Professor Dr. H. GUDDEN, Oberstabsärzt z. D. Dr. W. HASSLAUER, Privat-Dozent Dr. W. HEUCK, Stabsärzt Professor Dr. FR. SALZER, Oberstabsärzt Professor Dr. Gg. SITTMANN, Professor Dr. W. SPIELMEYER, Professor Dr. W. WEICHARDT. S. 238, mit einer Tabelle und 12 Abbildungen. München: J. F. Lehmann's Verlag.

UNLIKE the manual of war surgery by Delorme, which was recently reviewed in these columns, this little work was designed to serve as a *vade mecum* for the common diseases that are inseparable from camp-life. The subjects dealt with are exactly those which are encountered in the daily routine of a busy medical out-patient department. Thus, brief working abstracts are given, among the contagious diseases, of typhoid fever, grip, gonorrhea, lues, tetanus, etc.; among the thoracic diseases, of acute cardiac failure, functional heart disturbances, bronchitis, and tuberculosis; among nervous diseases, sunstroke and thermic fever, neuralgias, herpes zoster, neuritis, hematoma of the dura mater; among psychic disturbances, dementia precox, epilepsy, alcoholism, contusion psychoses and neuroses. The common affections of the eyes, ears, nose and skin are also covered in brief.

The book is eminently practical throughout, presents modern methods, and is useful in refreshing the memory on medical minutiæ.

P. G. S., JR.

DIE OPERATIVE BEHANDLUNG DER LUNGENTUBERKULOSE. Von Prof. Dr. F. JESSEN, Davos. Würzburger Abhandlungen aus dem Gesamtgebiert der praktischen Medizin. S. 56, mit 8 Abbildungen im Text. Würzburg: Verlag von Curt Kabitzsch.

THIS brochure serves a good purpose by pointing out to the practitioner the possibilities of the surgical treatment of pulmonary tuberculosis, when the cases are properly selected. There are considered in order extirpation of the tuberculous lung; the opening of cavities; artificial pneumothorax; extrapleural thoracoplasty; plugging of cavities and pleurolysis; phrenicotomy and stretching of sympathetic cord; ligation of pulmonary artery; and operations upon the superior aperture of the thorax. The greater part of the monograph is devoted to the consideration of artificial pneumothorax, and in this subject are included very instructive diagrams.

From the nature of the malady it holds that the results of the present-day operative treatment of pulmonary tuberculosis are not so favorable as surgery upon healthy patients has to offer; but the operative treatment enables one to help—even cure—many patients who without it would have succumbed. When the indications for operation are urgent, the risk in proportion to the amount of benefit that may be derived is very slight. The surgery of pulmonary tuberculosis needs further development, but has already become indispensable: it should be combined with general hygienic and dietetic tuberculous measures. As Sauerbruch once observed, advanced pulmonary tuberculosis is more of a mechanic than a constitutional bacterial problem. The hope of the future is to combine operative procedures with climatic and chemic treatment.

The brochure throughout gives a good outline of the present state of the operative treatment of pulmonary tuberculosis.

P. G. S., Jr.

Cancer of the Stomach. By Frank Smithies, M.D., Gastro-enterologist to Augustana Hospital, Chicago; formerly Gastro-enterologist to the Mayo Clinic, Rochester, Minn. With a chapter on the Surgical Treatment of Gastric Cancer. By Albert J. Ochsner, M.D., LL.D., F.R.C.S., Professor of Clinical Surgery in the School of Medicine of the University of Illinois. Pp. 522; 106 illustrations; 41 tables. Philadelphia: W. B. Saunders Company, 1916.

This book is undoubtedly the best contribution to the subject of gastric cancer that has as yet been published. While the author in his preface rightly admits that it is by no means the "last word" upon the subject, nevertheless it is the latest one.

The material for this book is based upon the study and analysis of 921 cases of cancer of the stomach largely from the Mayo Clinic at Rochester, Minn., and most important of all is the fact that each case studied has been operatively and pathologically proved to be cancer. The author is therefore dealing with facts and not fancies —facts that have been secured by painstaking perseverance and recorded in detail and the interpretation of these facts has been made by a clinician of wide experience and one whose interests are largely centred in the problems of the gastro-intestinal tract.

Furthermore, there has been a most happy coöperation between the clinician, the clinical and radiographic laboratories and the surgeon, a combination that is indispensable to the diagnosis of early cancer. Here may be mentioned the only criticism that is offered and that is the failure of the insertion of tables giving data as to surgical end-results. Here lies the proof of the pudding.

The book is divided into eleven chapters by Smithies, which completely cover the subject from the standpoint of etiology; morbid anatomy; symptomatology; physical examination; diagnostic laboratory tests; Roentgen examinations; differential diagnosis; non-surgical treatment and an especially important chapter on the significance of gastric ulcer with respect to gastric cancer. There is in addition one chapter ably handled by Ochsner on the surgical treatment of gastric cancer. All chapters are good. The morbid anatomy and diagnostic laboratory investigations are particularly well handled. In the chapter under symptomatology the author has made a notable contribution in dividing his cases into six groups with a differentiation of the types of case histories commonly met with. This is important and timely because the commonly accepted type is the classic text-book picture which applies to late rather than early cancer.

The book is printed on good paper, in large easily-read type, and the tables and illustrations are all good and have been selected and prepared with great care. One point to emphasize is the general readability of this monograph, and the author is to be congratulated upon his literary style.

This book should be in the hands of every practitioner who is interested in this subject, and could well be made a monographic text-book in our medical schools. B. B. V. L.

A Text-book upon the Pathogenic Bacteria and Protozoa. For Students of Medicine and Physicians. By Joseph McFarland, M.D., Professor of Pathology and Bacteriology in the Medico-Chirurgical College, Philadelphia. Eighth edition, thoroughly revised. Pp. 807; 323 illustrations, a number of them in colors. Philadelphia and London: W. B. Saunders Company.

The eighth edition of McFarland's deservedly popular book will be received with pleasure and profit by those accustomed to use the previous editions. The new edition appears in larger page form than the previous edition, indicating that the type has been reset, but sufficient material has been added to keep about the original number of pages. Many beautiful illustrations have been added.

Dr. McFarland has adhered to the division of his book into two parts, the first on general bacteriology and technic; the second devoted to special diseases. The chapter on bacterio-vaccines is not all that could be desired. There is not enough said of the practical application of vaccine therapy, and the only method given for counting a vaccine is the inaccurate method of Wright; direct counting in a blood counting chamber, or preferably in a special chamber such as the Helber is not even mentioned. The technic of the Wassermann reaction is not given with the clarity of style one finds in the rest of the book. It seems to the reviewer that a more detailed description of the various accepted technics would be an improvement. The space devoted to antiseptics and disinfectants and their use is well allotted; too often do we find these subjects and their practical application but skimmed over.

The second part of the book, devoted to special diseases and their germs, is presented as before in rather curious order. Toxic and endotoxic diseases, acute infections and protracted diseases, protozoal and bacterial—all are given together, with apparently no systematic arrangement. It would appear to be better to present the diseases according to some classification. It might not be amiss to devote a separate section to protozoal diseases.

The author is to be congratulated on the addition of some of the diseases due to filterable viruses in the new edition. As bacteriological and immunological methods are used in the study of these diseases it might be well to include all those conditions now attributed to filterable virus. H. F.

Diseases of the Throat, Nose and Ear. By William H. Kelson, M.D., B.S., F.R.C.S. (Eng.), Surgeon of the London Throat Hospital, Golden Square; Hon. Surgeon (Nose, Throat and Ear Department), City Dispensary; Lecturer on Diseases of the Ear. Pp. 252; 89 illustrations. London: Oxford Med. Press.

This work is a small text-book written for the general practitioner and the senior student. For this reason the more common and trivial procedures, such as the removal of cerumen, are given in considerable detail, while the more important undertakings, which are generally relegated to the specialist, are scarcely more than mentioned if not entirely omitted. We, however, see no reason why the author has failed to make any mention of such an important procedure as direct laryngoscopy and bronchoscopy. There is a lack of systematic arrangement of various subjects, and the style, to say the least, is exceedingly quaint. For instance, in speaking of pemphigus of the throat (p. 21) the author says "Arsenic has a great reputation in this disease but most of the patients die." On the whole the book is a rather trite accumulation of throat, nose and ear lore giving many of the well-established facts their proper importance, and yet, it is sufficiently full of mistakes, especially concerning pathology and therapeutics to make it a rather unsafe guide for either the student or medical practitioner. The illustrations while fairly numerous are not especially illuminating, and the majority are crude and uninteresting. G. B. W.

STUDENT'S TEXT-BOOK OF HYGIENE. By W. JAMES WILSON, M.D., D.Sc., D.P.H., Bacteriologist to the Counties of Down and Antrim; Lecturer in Hygiene and Public Health, Queen's University, Belfast. Pp. 270; 26 illustrations. New York: Rebman Company.

HYGIENE in a strict sense deals with the principles of the science of keeping well, while public health, preventive medicine, and sanitary science have to do with the application of those principles. It is in this strict sense of the word that Wilson takes up the subject of hygiene in this book. The details of laboratory methods, the procedures of public health administration, and the technic of prophylactic measures are wisely omitted. The application of the principles discussed is only indicated in sufficient degree to enable the student, for whom the book is primarily written, "to appreciate the meaning and value of the results of analyses, and to understand the responsibilities resting upon the medical officer of health, the general medical practitioner, and the private individual, with regard to the preservation of health and the prevention of disease."

One is surprised to note the author's statement that "the routine inoculation of contacts with prophylactic doses of diphtheria antitoxin is not a measure which recommends itself to many physicians at the present time." Also, "In the British Isles open fires find favor on account of their cheerful appearance, while in America stoves are almost invariably used." Furthermore, one would not expect typhoid fever to be given in the list of diseases for which isolation hospitals should be furnished. T. G. M.

PHYSIOLOGICAL CHEMISTRY. A TEXT-BOOK AND MANUAL FOR STUDENTS. By ALBERT P. MATHEWS, Ph.D. Pp. 1041; 78 text figures. New York: William Wood & Co.

MATHEWS has given us in this work one of the best books of its kind in physiological chemistry which has appeared in the English language in recent years. The author states in the introduction, "Some parts of this subject have been treated far more fully than others, and, possibly, more fully than their importance deserves." This might be considered a fault by some, but, as one's personal preferences guide him in his opinion, this could hardly be looked as upon a point for criticism. The book is divided into three parts: Part I deals with general properties of living matter: the usual separate chapters on carbohydrate, fat, protein, and a very interesting chapter on the physical chemistry of protoplasm. Part II deals with body heat, food, digestion, absorption, excretion, metabolism as a whole, and the various body tissues. Part III consists of practical work and methods. At the end of the important chapters there is found an excellent summary of the subject matter and also references to the literature. The subject matter is brought up to date and is presented in a lucid, fascinating, readable manner. The book is certainly to be recommended to students and others who are interested in biological chemistry. In view of the ever-increasing adaptability of biochemical methods in diagnosis the chapter on practical methods should certainly increase the value of this book to physicians. L. J.

LEJAR'S URGENT SURGERY. By FELIX LEJAR, Professor agrégé à la Faculté de Médecine de Paris; Chirurgien de l'Hôpital Saint Autaine; Membre de la Société de Chirurgie. Pp. 588; 1106 illustrations. Seventh edition, Vol. II. New York: Wm. Wood & Co.

THIS volume treats of the urgent surgery of the genito-urinary system, the rectum and anus, the hernias and the extremities. It is translated from the French by W. S. Dickie, M.D., and Ernest Ward, M.D.

The subject matter contained therein is all that could be desired. It treats of those phases of the conditions which are incompletely described and discussed in other works on surgery. No attempt is made to give a complete description of any one condition as regards pathology, etiology, etc. The reader is introduced to the urgent condition and then told how to handle it. Throughout the text there are numerous footnote histories of cases illustrating the condition under discussion.

After arriving at the diagnosis the author describes in minute detail the subsequent treatment, discussing the one or more possible ways of overcoming difficulties that may arise.

The illustrations and plates, aptly chosen and well executed, enhance the value of the work.

The style is exact, easy and pleasing, presenting facts, theories and opinions in an interesting and novel manner.

The book is well edited and the paper and printing are of the best.

When one takes up this work he is at once impressed by the author's vast and comprehensive grasp of his subjects, and by his unique and pleasing way of presenting such knowledge.

E. L. E.

SURGERY OF THE LUNG. By C. GARRÉ, Professor of Surgery at the University of Bonn, and H. QUINCKE, formerly Professor of Medicine at the University of Kiel. Translated from the German by DAVID M. BANCROFT, M.D. Second edition. Pp. 271; 114 illustrations and 2 colored plates. New York: William Wood & Co.

THE first edition of this work appeared in 1903, and since that time surgery of the lung has made such rapid progress that it has been necessary for the authors to alter and rewrite the subject matter to a considerable extent. Not only by constant and careful elaboration of the older methods of procedure have the operations then in vogue been more frequently, and, on the whole, more successfully carried out, but new methods have been invented and new indications laid down.

The authors very properly devote the opening chapters to a review of the topographical anatomy of the lung, and then discuss the all-important question of pneumothorax, the avoidance and treatment of which has been responsible for much of the advance in thoracic surgery.

In detailing the various methods of maintaining a difference of pressure, mention is made of the work of the pioneers in this field, whose original ideas have been followed by the brilliant discoveries of the investigators of the present day. The advantages and disadvantages of positive and negative pressure, and of the cabinets, apparatus, or masks producing the same, are described very concisely. It is frankly admitted by the author that a greater number of operations on the lung have been performed by him without than with the aid of differential pressure apparatus. As intratracheal anesthesia has been adopted so generally since the publication of this volume, further discussion of its safety and of its numerous advantages is unnecessary. The methods employed in general surgical technic and the treatment of pulmonary injuries and suppurations are brought up to date, and are well worth reading in view of the large number of recent contributions dealing with injuries of the lung occurring in the present war.

The treatment of pulmonary tuberculosis by artificial pneumothorax has become so general that the chapter devoted to this subject is of particular interest. The matter has been considered carefully in every detail and the technic accurately described. It would seem, however, that more emphasis could be laid upon certain of the dangers which may follow the production of the pneumothorax, particularly as many believe that the technic is simple and that preliminary training is unnecessary. The authors rightly conclude that statistics of the results of treatment with artificial pneumothorax are of little value because the condition of the patient was and always will be too diverse. Thus it becomes a question of how long the patient might have lived without the operation.

Trendelenburg's operation on embolism of the pulmonary arteries, the progress made of late years by the operative treatment of rigidity of the thorax in pulmonary emphysema, and the treatment of foreign bodies are all described, indicating that the volume includes the most recent measures employed in thoracic surgery. The work contains much information of interest to the practicing physician, and will prove to be of marked value to the operator accustomed to dealing with the difficulties arising in this new field of surgery. J. S.

WOUNDS OF THE THORAX IN WAR. By J. KEOGH MURPHY, M.D. Pp. 156; 19 illustrations and 2 plates. London: Oxford Med. Press, 1915.

WOUNDS of the thorax, produced by a great variety of weapons and missles, present unusual and difficult problems that civil practice does not prepare a surgeon to solve. The author supplements his large experience by studying the records of the Boer War, particularly the writings of Colonel Sir G. H. Makins. The volume deals with the clinical features of the various wounds, their immediate and remote effects and especially with therapeutic measures. The modern plan of treatment formulated by Sir Watson Cheyne, and that of Cheatte, Fildes and Rajschman are described as well as a summary of Sir Almoth Wright's recent conclusions regarding vaccine therapy. G. M. L.

NOTICE.—In the review of "Serology of Nervous and Mental Diseases," by D. M. Kaplan, published on page 902 of the June issue of the JOURNAL, note should have been made in the title that the book is published by W. B. Saunders Company, Philadelphia and London.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Pyloric Exclusion.—Lewisohn (*Surg., Gynec. and Obst.*, 1916, xxii) says the vast majority of surgeons agree that pyloric exclusion ought to be added to gastrojejunostomy to insure the permanent cure of pyloric and duodenal ulcers. There still exists, however, a great difference of opinion as to the best method of accomplishing this exclusion. Lewisohn carried out a series of experiments on dogs to determine, particularly, the value of the following modification of Biondi's method: After the gastro-enterostomy is done, the gastrohepatic ligament is ligated in the pyloric region, which enables us to deliver the pylorus in front of the abdominal wall. A transverse incision through the seromuscularis is then carried around the pylorus. The muscularis is peeled away from the mucosa which is thus exposed intact for about one inch. The mucosal tube is ligated above and below with a silk or Pagenstecher ligature, cut in between the ligatures and the stumps carbolized. The stumps are then buried by suturing over them the previously reflected seromuscularis layer. Lewisohn concludes that with the exception of Eiselsberg's unilateral exclusion and the modified Biondi method none of the different methods of exclusion guarantees a permanent exclusion of the pylorus. An absolute though temporary exclusion of the pylorus provides for a permanent cure of pyloric and duodenal ulcers. The most simple method from a technical standpoint is the exclusion stitch (Kelling-Berg-Cackovic). This stitch should be used in preference to the more complicated methods (Wilms, Parlavecchio, Biondi). The Eiselsberg's method and the modification of the Biondi method, though guaranteeing a permanent exclusion, are technically too complicated and should not be used. The clinical results are just as good in using the most simple method (exclusion stitch) as in the use of the most complicated method (Eiselsberg). The exclusion stitch is, therefore, the method of choice for the treatment of pyloric and duodenal ulcers. It is carried out as follows: A double Pagenstecher linen suture, armed with a needle, is carried around the posterior stomach wall, and is held in place by taking several bites in the anterior wall of the stomach. The suture is then tied and the pylorus thus occluded.

Rectal Drainage of Appendiceal Pelvic Abscess.—Schrager (*Surg. Gynec. and Obst.*, 1916, xxii, 482) reports 4 cases in which appendicular pelvic abscesses were drained by the rectum. In 3 of the 4 cases the collections of pus were secondary to a preceding operation for appendicitis and needed most dependent drainage. All 4 cases did very well after the rectal drainage was provided. Some of these abscesses if left alone will perforate into the rectum and thus be cured. He says that rectal examination is a valuable aid in the diagnosis of acute inflammatory processes of the lower abdomen. A number of cases of acute appendicitis are either associated with or followed later on by pelvic abscesses, some of them pointing into the rectum. Rectal drainage of appendicular abscess is a simple procedure and can be resorted to in emergencies even by less experienced surgeons. Cases of suppurative appendicitis convalescing badly occasionally do so because the dependent abscess is not drained. In desperate as well as suitable cases, rectal drainage is a very gratifying procedure. Dr. Ochsner's technic was given as follows: Either gas or ether may be used, although in adults gas is preferable. The patient is placed in the lithotomy position well brought down over the edge of the table. The sphincter is next dilated until it is completely paralyzed. Ether is more suitable for this step than gas. Two long-bladed, right angle, flat retractors are next introduced into the rectum, depressing the upper and lower rectal walls. If the diagnosis is correct, the fluctuating mass soon appears in view, being covered by a smooth, shining rectal mucosa. A small incision is made with scissors or knife in the anterior rectal wall and a sharp pointed forceps, dressing forceps, or the blade of scissors is introduced through this button hole. A rubber tube is then inserted high up into the rectum while another one is introduced into the abscess cavity, thus preventing the feces from entering into it. The tubes escape or are removed in a few days and there is no after-treatment.

Loose Bodies in the Knee-joint.—Henderson (*Amer. Jour. Orthop. Surg.*, 1916, xiv, 265) classifies these bodies into (1) fibrinous loose bodies; (2) bodies composed of organized connective tissue, *e. g.*, bone and cartilage, intrinsic in origin; (3) loose foreign bodies, extrinsic in origin. The fibrinous bodies have been variously named according to their size, as melon seeds, rice bodies, wafer bodies, etc. They are not confined to joints, but are often seen in bursæ and in tendon sheaths, and are thought to be pathognomonic of tuberculosis. An hypertrophied fat tag may cause trouble, but Henderson has rarely seen such a case and in none of the cases which he reports was the operation done for the relief of such a condition *per se*. Organized connective tissue loose bodies produce mechanical derangements. They are usually spoken of as being cartilaginous, but frequently on section there will be seen a flake of bone. In Henderson's experience the majority of these bodies have arisen from the internal condylar surface of the femur. They may be further subdivided into (*a*) those having as their etiological factor some disease such as osteoarthritis or Charcot's disease, and (*b*) those due to injury. Both kinds are inseparable in certain cases. A comparatively slight trauma might produce a loose body in a person affected with osteochondritis dissecans, whereas the same trouble in a normal person would not be productive of trouble. Because it is difficult to determine the degree of indirect trauma necessary to produce the loose bodies in this group, they had better be considered as due to trauma rather than to an actual disease. Trauma, direct or indirect, is essential to the production of a loose body. Surgery offers the only permanent relief, and the general condition of the patient being satisfactory, the bodies should be removed.

Preoperative Treatment of the Hands.—WHITING and SLOCUM (*Ann. Surg.*, 1916, lxiii, 608) conducted investigations at the German Hospital, Philadelphia, to determine a method of hand sterilization that would approach the ideal, be simple in application and allow of more rapid execution. As a result of these investigations they concluded that none of the various solutions used will destroy all germs of the skin in all instances, but that a solution of acetone, alcohol, and one of the coal tar disinfectants of a high phenol coefficient is more efficient than any other agent they have used for skin sterilization. In such a solution the acetone (dimethyl ketone) acts as a solvent of the fatty or oily material of the skin and thus aids in exposing the bacteria to the germicides. The alcohol acts as a solvent; it has the power to penetrate into the cracks and crevices of the skin, as claimed by Braatz, through its ability to destroy and remove small particles of air that may be present; it is germicidal in solutions as weak as 30 per cent., according to Post and Nicoll, in solutions ranging from 40 per cent. to 95 per cent., according to the findings of the authors, with its strongest germicidal powers in solutions ranging from 60 per cent. to 70 per cent., according to Leedom-Greene; it also acts as a good vehicle. The coal tar disinfectant that may be used acts simply as a powerful germicide, destroying all bacteria with which it comes in contact in a length of time varying with its coefficient and the degree of dilution. Patients do not complain of any irritation following the use of this solution, although it causes a burning sensation when used on the scrotum. It does not stain the skin. It reduces to a minimum the time consumed in preparing the field of operation, and its method of application is the simplest. It may be used on a wet or dry skin when necessary. There is no exfoliation of the skin as after iodine nor is there any blistering. It is suggested that a solution consisting of 35 per cent. acetone, 1 or 2 per cent. of a coal-tar disinfectant of a high coefficient, preferably phenoco, with enough alcohol to make 100 per cent., would answer the purpose best. The method of application consists in rubbing the field. of operation for two minutes with a piece of gauze saturated with the solution after either a wet or dry shave. A warm, cleansing tub bath is, of course, always advisable when not contraindicated.

Final Results in Twelve Cases of Colectomy.—Clark (*Surg., Gynec. and Obst.*, 1916, xxii, 533), in referring to Lane's most recent book on intestinal stasis, says that it is not the occasional brilliant result that counts in a work of this unusual character, but it is the analysis of all of the cases that have come under the operator's care, with full histories and a painstaking follow-up record system, that permits the reader to bring his own judgment to bear on this very important subject. In only 6 of the 12 cases operated on, by Clark, may one consider the result as entirely satisfactory. In all cases there has been great improvement in the constipation for a time, to be followed at variable intervals in four by a gradual recurrence of the constipation. In some cases this has not been so severe as formerly, whereas in others it is quite as intense. Roentgen-ray examinations in 3 cases showed in 2 decided dilatation of the ileum to a size closely resembling that of the colon. In none of these cases has there been diarrhea of long standing, and none that was not controlled by simple medicinal measures. In none of the cases has there been undue thirst. In 6 cases there has been marked improvement in nutrition. In the remainder there was no visible effects so far as physical improvement is concerned. As a final summary of these cases, Clark feels that total removal of the colon is justifiable only in severe cases of obstructive constipation. From his experience in these 12 cases he is of the opinion that a less radical procedure must be employed, and inclines to the limitation of the colectomy to the ascending and the middle of the transverse colon, with a lateral anastomosis of the ileum into the transverse colon. In this way the omentum is preserved, and there is less traumatism to the mesentery, with its very important sympathetic nervous system. Any form of anastomosis between different segments of the colon or between the cecum and sigmoid flexure, with the expectation of diverting the fecal current into this new channel, will almost invariably be doomed to failure. Finally, he believes that the one valuable point gained in the study of his cases of colectomy is that the ileum will not uniformly assume the vicarious function of the colon, and that the backward pressure from the colon, through the anastomotic opening, when it is low down, in definite proportion of cases causes dilatation and permanent impairment of the ileum. If a technic can be devised that will prevent the reflux into the ileum it will serve a splendid purpose in obviating one of the objections to an extensive colectomy. In severe cases of obstructive constipation it may be a very efficacious operation if carefully restricted and may be added to our therapeutic list. The immediate danger of the operation and the serious sequelæ that may follow weeks or months later make it, however, too hazardous to extend it into wider fields so ardently advocated by Lane and his enthusiastic followers. It may be efficacious, but it possesses no miraculous function.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

Influence of Some Drugs Used in Treatment of Gout.—Denis (*Jour. Pharm. and Exper. Ther.*, 1915, vii, 601) says that sodium benzoate, atophan and the salicylates including aspirin, when given in sufficiently large amounts cause an increased elimination of uric acid from the blood. This effect lends some support to the view that the good effects produced by the drugs at present considered by clinicians as most efficient in the treatment of gout may in part at least be due to a power possessed by them of producing a lowered kidney threshold for certain specific substances. Atophan and the salicylates possess this power in a marked degree. Benzoic acid when administered in large doses (8 gm. per day) increases the uric acid excretion in the urine and decreases the uric acid content of the blood. Cinnamic acid in the comparatively small doses used (4 to 6 gm. per day) have little, if any, effect. Quinic acid and colchicum have also no effect on the uric acid elimination. The same is true of para-oxybenzoic acid which shows none of the power possessed by its homologue, salicylic acid, of producing a lowered kidney threshold for uric acid. None of these drugs produce any change in the non-protein nitrogen content of the blood. Benzoic acid, aspirin and atophan were found to have no effect on the creatin content of the blood.

The Uric Acid Solvent Power of Urine After Administration of Piperazin, Lysidin, Lithium Carbonate and other Alkalies.—Haskins (*Arch. Int. Med.*, 1916, xvii, 405) found that piperazin can cause the urine to dissolve more uric acid than it would without the drug, and this effect is most marked if sodium citrate or bicarbonate be also given and if diuresis be avoided. Lysidin can act as a uric acid solvent but is not a practical therapeutic agent because of the large doses required. Lithium carbonate is a uric solvent if large enough doses are used, but is unsafe and possesses no advantage over sodium citrate or bicarbonate. Sodium citrate and bicarbonate are reliable and satisfactory uric acid dissolving agents when given in such dosage as to keep the urine alkaline.

The Standardization of Digitalis and the Potency of American-grown Digitalis.—Rowntree and Macht (*Jour. Amer. Med. Assn.*, 1916, lxvi, 870) relate their investigations which strikingly emphasize the need of standardization of digitalis. Variations in lethal dose from 6.6 to 19 c.c. per kilogram weight, approximately 300 per cent., were found in the infusions prepared from digitalis leaves of different sources. This difference is greater than should be tolerated by the profession. The different leaves tested by the authors were all obtained from very reliable sources, and in all probability greater variations exist in leaves purchased in the open market. The authors emphasize that standardization reveals the strength of the digitalis preparation and permits of graded dosage—more or less—according to the potency of the preparation. The physician's duty to his patient does not end with the prescribing of digitalis. Plainly it is incumbent on him to secure digitalis effects if the case is a suitable one. This is more likely to be accomplished if the potency of the preparation is known. It is especially interesting at this time to find that certain American-grown digitalis leaves yielded a product superior in potency to those made from English and German leaves.

Remarks on Bacillus Welchii in the Stools of Pellagrins.—HOLMES (*Arch. Int. Med.*, 1916, xvii, 453) says that B. welchii has been found with marked regularity in the stools of pellagrins in numbers greater than normal. These pellagrins were on a dietary composed principally of vegetable foods high in carbohydrate content. The diet was extremely low in protein and especially in protein of animal origin. Holmes notes the facts that diarrhea is one of the most constant symptoms of the disease known as pellagra and that B. welchii has been found to produce severe diarrhea in children and adults in the presence of a high carbohydrate diet. Furthermore, diarrhea caused by B. welchii can be cured by a protein and buttermilk diet. The authoı calls attention to the fact that Goldberger has prevented pellagra by the addition of proteins and buttermilk in the diet, and has experimentally caused pellagra by means of a pure carbohydrate diet. He believes that the above facts by no means prove that B. welchii is the direct or sole cause of pellagra but believes their coincidence is sufficiently significant to justify further observation.

Venesection as a Therapeutic Measure.—LAWRENCE (*Bost. Med. and Surg. Jour.*, 1916, clxxiv, 203) says that venesection performed under proper indications, is not a dangerous measure, especially since the "dose" can be accurately controlled. In the presence of dilatation of the heart, renal toxemia, hypertension or a combination of these conditions, it may be expected to act more promptly and more surely than drugs. It lowers blood-pressure and at the same time produces a more efficient circulation when performed in cases of hypertension, but does not, in therapeutic "doses" lower normal arterial tension. Venesection should never be performed in the absence of definite indications, but should not be withheld until the hope of success from any measure is gone. The amount of blood to be withdrawn is to be decided by the point at which relief is to be obtained. The error is generally on the side of removing too small an amount. Repeated blood-letting, when indicated, does not seem to have any ill effects upon the composition of the blood.

Corpus Luteum Extract in the Nausea of Pregnancy.—HIRST (*Jour. Amer. Med. Assn.*, 1916, lxvi, 645) reports encouraging results with the hypodermic administration of corpus luteum extract for the treatment of nausea occurring in pregnancy. He bases this treatment on the presumption that there is more than a coincidence between the formation and disappearance of the corpus luteum of pregnancy and the cessation of the nausea. Only five cases are reported, four of which were successfully treated. Hirst makes this preliminary report in the hope that this treatment may be tried by others in order to determine whether or not it is of value.

Pellagra—Causation and a Method of Prevention.—GOLDBERGER (*Jour. Amer. Med. Assn.*, 1916, lxvi, 471), in a summary of his observations made in three institutions where pellagra was endemic, states that a diet containing a liberal amount of fresh animal and leguminous protein foods, without other alteration in the hygienic and sanitary conditions, successfully prevented the annual recurrence of the disease in practically 100 per cent. of the cases. Of the 209 cases of pellagra observed at the two orphanages during the spring and summer of 1914, not less than 172 completed at least the anniversary date of their attack under observation. In only one of these 172 cases, following the change in diet, was there recognized evidence of a recurrence, although on the basis of experience elsewhere, from 99 to 130 might reasonably have been expected. Nor was any new case observed among the non-pellagrin residents, 168 of whom completed not less than one year under observation. Of the group of pellagrins on the modified diet at the insane asylum, 72 remained continuously under observation up to October 1, 1915, or at least until after the anniversary date of their attack of 1914. Not one of this group has presented recognizable evidence of a recurrence, although, of a group of thirty-two controls, fifteen have had recurrences. Pellagra may, therefore, be prevented by an appropriate diet without any alteration in the environment, hygienic or sanitary, including the water supply. At an isolated convict camp, previously free from pellagra, with an average population of from seventy to eighty white males, eleven volunteers were segregated and, after a preliminary observation period of two and a half months, placed on an abundant but one-sided, chiefly carbohydrate (wheat, corn, rice) diet, from which fresh animal proteins and legumes were excluded. At least six of these volunteers developed pellagra. This result would appear to have been brought about by the diet on which they subsisted. A definite conclusion as to the intimate mechanism involved in bringing about or in preventing the disease by diet cannot be drawn from the available data. For the practical purposes of preventive medicine it would seem to be of fundamental importance to recognize that the pellagra-producing dietary "fault" is capable of correction or prevention by including in the diet suitable proportions of the fresh animal and leguminous protein foods.

The Intraspinal Administration of Mercurialized Serum.—HUNT (*Jour. Am. Med. Assn.*, 1916, lxvi, 404) reports a series of 45 cases of which 40 were given intraspinal injections of mercuric chlorid, and 5 were given sublamin injections. These patients were at the same time given intramuscular injections of mercuric salicylate every week, and in the very early ones intravenous injections of salvarsan. The cases treated comprised cases of tabes, general paresis, cerebrospinal syphilis, taboparesis, clinical tabes (tabes with a negative serology) and syphilitic hemiplegia. These patients were observed over a period of six months and Hunt believes that the number of cases is too small and the period of observation too short to draw any definite conclusion. The author found that the reaction from mercuric chlorid or sublamin in no way differed from the reaction which followed the administration of salvarsan. The sublamin did not seem to give the same reduction in the cell count or clinical improvement as did the mercuric chlorid. No ill results followed these injections. The three deaths could be easily accounted for, as the patients were practically moribund at the time of the treatment, and were given the injections as a last resort. The patients with tabes and cerebrospinal syphilis were helped more than any others. The ten patients with general paresis treated showed less improvement than almost any of the others. One-half of them showed no change and two became worse. Such improvement as did occur was evident in the feelings of the patient, in the sphincter control, in the pains, in the gait, and in the serology. There was no improvement in the reflexes. Such intraspinal treatment can be given only at intervals of two weeks, because a cell count does not fall sooner. The reaction obtained was one in which the cell count was first greatly increased and then diminished. The cell count and the globulin yielded much sooner than did the Wassermann.

The Treatment of Central Nervous System Syphilis.—Walker (*Boston Med. and Surg. Jour.*, 1916, clxxiv, 195) summarizes the treatment and results in the first 40 cases of central nervous system syphilis at the Peter Bent Brigham Hospital. This group includes cases of tabes, general paresis, cerebrospinal syphilis and syphilitic meningitis; cases of purely cerebral syphilis are excluded. In the treatment of parasyphilis three methods were employed: one, salvarsan, intravenously alone; another, the Swift-Ellis method; and a third, salvarsanized serum alone intraspinally. Walker used large doses of salvarsan intravenously for those cases treated with salvarsan alone; in those treated with serum intraspinally 20 to 25 c.c. of undiluted serum were used. It was found that cases of syphilis of the central nervous system with only a positive blood react well to salvarsan; those with a positive blood and spinal fluid may react well to salvarsan alone, but they do much better when intraspinal serum is used in conjunction with salvarsan, and some who do not react to salvarsan alone do react well to the combined method. One may obtain improvement in general paresis with the combined treatment. Cases of syphilitic meningitis may clear up with salvarsan alone but the combined treatment is the quickest. Cases of central nervous system syphilis with a negative blood and positive spinal fluid findings react readily to salvarsanized serum intraspinally alone, even when salvarsan intravenously has failed. The spinal fluid of the cases treated with salvarsan has become negative in two cases, whereas the spinal fluid of seven cases treated with the serum alone has become negative. The author feels that salvarsanized serum is a great asset in the treatment of syphilis of the central nervous system, and in the general run of cases he thinks the Swift-Ellis method is of great value and that this method in conjunction with mercury given intramuscularly is the best treatment of syphilis of the central nervous system at the present time. Marked improvement always follows such treatment.

The Comparative Pharmacological Action of Ethylhydrocuprein (Aptochin) and Quinin.—Smith and Fantus (*Jour. of Pharm. and Exper. Ther.*, 1916, viii, 53) call attention to some facts regarding optochin which are important because of the increasing use of the remedy for the treatment of pneumonia. Optochin is an alkaloid derived from cuprea bark and in its chemical structure is closely related to quinin. While quinin chemically is methoxycinchonin, optochin is a hydroxycinchonin. Morgenroth, in 1911, reported that he was able to protect over 90 per cent. of animals against artificial pneumococcus infection by injections of optochin. His work has been confirmed by others and particularly of late many favorable reports have been made regarding its therapeutic use in lobar pneumonia. The authors found that the pharmacological action of optochin is qualitatively like that of quinin, but differs in degree. Optochin is more toxic than quinin. In view of its considerable degree of toxicity, the authors urge caution in the clinical use of optochin, especially in its intravenous administration. They found that when administered intravenously it lowers the blood-pressure somewhat less than quinin although it depresses the heart more. The peripheral vasoconstriction probably counteracts partly the effects of cardiac depression. Optochin was not so efficient an antipyretic as quinin in experimental fever of animals. Optochin has been advocated for local use in eye infections, particularly those due to the pneumococcus, but the authors found that even a 2 per cent. solution was highly irritant to the conjunctiva.

The Treatment of Typhoid Fever by Intravenous Injections of Polyvalent Sensitized Vaccine Sediment.—Gay and Chickering (*Arch. Int. Med.*, 1916, xvii, 303) report a series of 53 cases of typhoid fever, in which the diagnosis was absolutely certain both on clinical and on laboratory grounds, treated by intravenous injections of a sensitized polyvalent typhoid vaccine. These patients were cared for under varying conditions in private houses and hospitals. The mortality in these cases has been precisely what one would expect under the best hospital conditions (9 per cent.), which the authors regard as suggesting that, under uniform conditions, with their method of treatment the mortality would have been less than the average. The mortality has been composed, to a large extent, of what may be termed "accidents" of typhoid, namely 60 per cent. of deaths by hemorrhage or perforation. Their method of treatment has consisted in the intravenous injection of $\frac{1}{50}$ to $\frac{1}{25}$ mg. (150 to 300 million bacteria) of a sensitized, polyvalent, killed typhoid vaccine sediment prepared after the method of Gay and Claypole. This injection gives rise to a series of symptoms characterized particularly by a chill, rise and fall of temperature, and leukopenia followed by hyperleukocytosis. The fall of temperature with its attendant hyperleukocytosis leaves the patient at least temporarily benefited, and the benefit and normal temperature may be permanent. Thus in 66 per cent. of the cases a distinct benefit was obtained, as shown by lowered temperature, disappearance or amelioration of subjective symptoms and an apparently accelerated recovery. In 41.5 per cent. of this 66 per cent. the recovery was of an abortive form with a critical fall of temperature and a permanent normal temperature established within a few days. This permanent normal temperature was reached on an average seven days after beginning treatment in these cases. There remains, however, 34 per cent. of cases which are classified as relatively unaffected. They regard this classification as underestimating the beneficial results for reasons given. In none of the cases did the use of the vaccine have any apparent harmful effect on the case, although in four, in which too large a dose was used, the symptoms were somewhat alarming. A series of subcutaneous injections following the intravenous treatment apparently aids in preventing relapses. The authors regard the mechanism of benefit and cure in these cases which were affected by the treatment as due to a combination of specific hyperleukocytosis and the presence of antibodies in the patient's blood. The injection of vaccine could be shown in a number of cases to be followed by the disappearance or diminution of bacteremia and usually also by an increase in the Widal. In those cases which did best the Widal was originally high and those cases which showed the least effect had the low Widals. The cases judged as "mild" before treatment began did better on the whole than those regarded as "severe." There were, however, a number of severe cases which showed abrupt recovery or benefit. On the hypothesis that successful results are due to the strength of the antibodies already established in the patient, Gay and Chickering ventured in severe cases with low antibody content, to combine with the vaccine treatment the intravenous injection of considerable amounts of typhoid immune serum from goats. These cases, although few in number, suggest that this type of treatment with further elaboration might increase the percentage of favorable results. They regard the use of sensitized vaccine as being better for intravenous injection than plain typhoid vaccine or less specific methods of treatment that have been suggested by other authors, owing to the fact that sensitized typhoid vaccine produces a specific form of hyperleukocytosis of maximum degree (Gay and Claypole), and may also be shown to be followed by an increase in active immunity of the patient against the disease.

The Intravenous Administration of Mercury in Syphilis.—SHAW (*Med. Record*, 1916, lxxxix, 823) reports 16 cases of syphilis treated by intravenous injections of mercuric chlorid with good results. The dose used was $\frac{1}{8}$ to $\frac{1}{6}$ of a grain to a patient of 140 to 150 pounds body weight, every five to seven days. Shaw says that this method is quick, safe and certain; the dose can be very accurately measured and the administration is free from pain. The therapeutic effects are just as quick, in many cases more certain and more permanent than those following salvarsan and neosalvarsan. This method is recommended also because of its availability and cheapness. The administration is attended with no untoward results except for a low grade of phlebitis which may produce obliteration of the vein used and which is in proportion to the concentration of the solution used.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND FREDERICK O. WAAGÉ, M.D.,

OF PHILADELPHIA.

The Schick Test in an Orphan Asylum.—Stearns S. Bullen (*New York State Jour. Med.*, 1916, xvi, 208) reports the results of the Schick test on 132 normal, healthy children at the Rochester Orphan Asylum. Of this number, 100 were again tested one year later. On both occasions the toxin was diluted with normal saline solution, so that the required amount ($\frac{1}{50}$ minimum lethal dose for the guinea-pig) was contained in 2 c.c. The children averaged from two to seventeen years in age. The injections were attended with practically no pain or distress. On both tests practically 55 per cent. of the children gave a negative reaction, showing that they had sufficient natural antitoxin in their tissues to neutralize the toxin injected, that is, at least $\frac{1}{30}$ unit per cubic centimeter of serum, sufficient to protect against diphtheria. Immunization was attempted on 41 children, with strongly positive reactions, by injecting subcutaneously, on two occasions with a four-day interval, $\frac{1}{4}$ c.c. of a toxin-antitoxin mixture. Of this number 35 still remained in the asylum eleven months later, and on being again tested still gave strongly positive reactions, showing they had developed little if any antitoxin as a result of the treatment. Eighteen children who gave positive reactions in May, 1914, showed no reaction in April, 1915. Fifteen children who gave no reaction at the first test showed more or less strongly marked reaction at the second test. Positive or negative results with this test do not give us data which remain the same for an indefinite period of time, one or two months at the outside being the limit. The test, which should be repeated at least once a month during an epidemic, in conjunction with the singling out of "carriers" by throat culture, allows epidemics in institutions to be controlled at about half the expense for antitoxin and with much less discomfort to the children.

Nephritis without Albuminuria.—J. Porter Parkinson (*Brit. Jour. Child. Dis.*, 1916, xiii, 138) reports a case of pneumonia in a boy, aged three and one-half years, which was followed by all the signs and evidences of nephritis, except that no albumin could be found in the urine at any time. Seven days after an uneventful recovery from the pneumonia he developed extreme swelling of the face, arms, hands, feet, legs, and the wall of the trunk. There was no sign of fluid in the chest or abdomen. Daily examination of the urine showed no albumin, but a few hyaline and granular casts and an occasional red corpuscle. The daily amount of urine was normal and contained fairly abundant urates. The blood-pressure was 90 mm. After four days of hot-air baths and purgatives the edema began to disappear, and in ten days all casts and blood had disappeared from the urine, and a week later the case was discharged as cured. The author believes the case to have been one of acute nephritis without albuminuria, but not probably induced by the pneumococcus which usually shows severe hematuria and abundant organisms in the urine which were absent in this case. The majority of cases of nephritis with edema and without albuminuria seem to be a result of scarlet fever, but in this case there was only an acute pneumonia. The absence of albumin in such cases causes many of them to be overlooked in the absence of careful microscopic examination. From the reports of Ballico, Herbert and others, cases showing casts and erythrocytes and no albumin may show no other signs of nephritis or may show only headache, pallor and fatigue. The author calls attention to the report of Philippe, in 1864, who claimed 60 cases of scarlatinal nephritis in which no albumin appeared, and the thesis of F. Leonetti, 1914, who reported a number of cases of nephritis in English soldiers with all the clinical signs except albuminuria.

Factors in the Incidence and Fatality of Measles.—J. G. Wilson (*Arch. Pediat.*, 1916, xxxiii, 261), from a study of statistics, shows that the mortality from measles is less than was considered correct some years ago. In New York City, in 1913, the mortality rate was 2.15 per 100, and in 1914 the rate for 28 States and Territories was 1.73 per cent., so that at present the case mortality rate of measles throughout the United States is less than 2 per cent. This, however, represents the low-water mark of measles mortality, as indicated by the mortality statistics compiled by a large insurance company two years ago, which showed a much higher mortality than has prevailed since the compilation was made. The mortality rate in measles is almost uniformly higher in institutions than in private practice and runs from 13 per cent. to 30 per cent. in large institutions generally. The Contagious Disease Hospital at Ellis Island showed a mortality from measles of less than 10 per cent. before the war, and for the last three months only 8.5 per cent. It is evident, therefore, that the disease has no fixed mortality rate, due probably to some as yet undetermined factor. A regular, periodical recurrence of measles epidemics has been noted in many cities, the time interval being about two years in New York City. The theory of the successive susceptible crops of individuals will not explain the periodicity of epidemics which is shown to vary in different places. Only one factor seems to bear a causal relation, and that is overcrowding. Suppurative otitis media, bronchopneumonia, and cross-infection are noted as the most important complications. Data are taken from the hospital at Ellis Island, and cover 2000 cases of measles. During a period of three years measles was four times as frequent as all the other contagious diseases combined. The influence of season on the development of bronchopneumonia seems small. Generally speaking every recovery from measles and bronchopneumonia is balanced by a death from measles with some other complication.

The Wassermann Reaction in Mental Deficiency in Children.—Alfred Gordon (*Arch. Pediat.*, 1916, xxxiii, 273), in a study of 78 cases presenting mental defects of varying degrees, makes the following points as regards hereditary syphilis: Even in the absence of all external evidences in child and parents, every case of mental abnormality in children should be investigated from the stand-point of hereditary syphilis. When hereditary syphilis causes extensive deformities or actual malformations of the central nervous system or other organs therapeutic endeavors are baseless and in vain. But when there is only feeble-mindedness of various degrees, and when this is associated with epilepsy, tremors or choreiform movements, or frequent and persistent headaches or where there are neurotic phenomena such as outbreaks of anger, of violence or tendency to vicious habits, then encouraging results may be obtained from methods based on the newer serologic investigations. In the series of 78 cases comprising imbeciles, idiots and feeble-minded with epilepsy, petit mal, headaches and those without functional or organic disorders the Wassermann test showed that 50 per cent. presented a positive reaction. While syphilis causes permanently defective offspring it also causes mental deficiency which is amenable to improvement. The detection of such recoverable cases is of paramount value. A negative Wassermann result should be followed by repeated tests at intervals. A positive result should be followed by vigorous and prolonged treatment by antisyphilitic remedies. Children up to the age of five were given mercurials and iodids. From that age on the treatment commenced with neosalvarsan, then continued with mercury and the iodids. The intraspinal method of salvarsanized serum was used exclusively on children of fifteen and sixteen years and supplemented by mercury and iodids. Mercury was given exclusively by inunction. The cases with organic changes were unresponsive. The feeble-minded showed decided improvement, in some, epileptic attacks diminished or ceased, those with petit mal especially showed improvement and the mentality in all these functional conditions showed striking improvement. The most striking improvement was in the feeble-minded with no functional disturbance.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Ultraviolet Rays in the Treatment of Pelvic Inflammation.—A few months ago we discussed in this department some work done by Fromme, of Berlin, in the treatment of chronic pelvic inflammatory conditions by means of ultraviolet light from the mercury vapor lamp. A recent report of similar work carried on in New York has recently been published by HELLMAN (*Am. Jour. Obst.*, 1916, lxxiii, 662), a former pupil of Fromme. The technic was apparently identical: the apparatus used is the "künstliche Hohensonnelampe" designed by Bach and Nagelschmidt; the source of light is a "transparent quartz tube, $\frac{8}{12}$ cm. long, on the ends of which are two transverse tubes which contain the mercury electrodes. The electrode vessels are provided with fan-shaped coolers with which the heat loss and therefore the current consumption is regulated. On each electrode between the coolers is situated the beaded lead which conducts the current to the lamp." The latter is enclosed in a suitable container, by means of which the amount of light permitted to pass can be regulated, the whole being easily adjustable up and down. The quartz glass used is of such quality as not to absorb any of the ultraviolet rays, upon which the therapeutic effects are believed to depend. The patient is placed before the lamp in a reclining position, the part of the body to be rayed being exposed, and the rest covered with a thin sheet. The eyes of the patient and of any one else in the room must be protected by dark glasses. The exposures vary from a minute and a half, with the lamp at a distance of 75 cm. at first, to twenty minutes at a distance of 40 cm. after a couple of dozen treatments have been given. Usually at least a day is allowed to intervene between two treatments; it is generally found that brunettes can stand longer exposures at the beginning than blondes.

Hellman reports the results in 8 cases of pelvic inflammation; all these were treated as ambulatory patients, without any other therapeutic measures. All eight have been examined recently and are apparently well, but only a short time has elapsed since the completion of treatment. While admitting that these eight, with the twenty-five cases previously reported by Fromme, are much too few from which to draw any definite conclusions, the author considers that "they do show however, that with this harmless technic some astounding results have been claimed and that these results are worthy of investigation whenever this kind of material presents itself. Certainly this mercury-quartz lamp should be tried in every case of pelvic inflammation of the subacute and chronic variety before operation is advised, and especially if the more commonly known methods have failed." In the discussion which followed the presentation of this paper before the Obstetrical and Gynecological Section of the New York Academy of Medicine, the majority of the speakers emphasized the marked improvement that is often seen in cases of this sort in time if let alone, and not subjected to too much meddlesome local treatment; if it does nothing more than accomplish this end, the light treatment may be of real value, although it cannot be denied that it may have a stimulating effect on the circulation and thus tend to aid in the resorption of exudates and diminution of inflammatory processes.

Tuberculin Treatment of Renal Tuberculosis.—Notwithstanding the fact that surgeons of experience are practically unanimous in the opinion that medical treatment has no place in tuberculosis of the kidneys, provided the diagnosis is definitely made while the case is in an operable stage and there are no special contraindications, the profession as a whole is as yet apparently far from being convinced upon this point. A recent report by HYMAN (*Jour. Am. Med. Assn.*, 1916, lxvi, 1379) upon the treatment of genito-urinary tuberculosis with Rosenbach's tuberculin is therefore of considerable interest. In 1910 Rosenbach described a new tuberculin, and reported a number of successful results of its application in the treatment of surgical tuberculosis, and since then several articles have appeared in the German literature substantiating Rosenbach's claims. Only one case had been described, however, in which the treatment was used in renal tuberculosis, and the report upon this was too meagre to permit of any conclusions being drawn. Hyman therefore undertook in a series of 13 cases of postoperative and of inoperable tuberculosis of the genito-urinary organs to try out this substance, which is a product of the symbiosis of the tubercle bacillus and the Tricophyton holosericum album. Its toxicity is considerably less than that of other tuberculins, so that much larger doses may be given. It is injected either locally into the diseased part or subcutaneously in an initial dose of from 0.01 to 0.1 c.c. this amount being successively increased by 0.1 c.c. unless a severe reaction ensues. As a rule injections are given every three to seven days, according to the severity of reaction produced. The maximum dose should not exceed 1.5 c.c., a total of 40 to 60 c.c., generally constituting the course of treatment. Of the 13 patients treated by Hyman, only 2 showed any improvement whatever; all the others were absolutely unimproved, and a few developed additional tuberculous foci during the course of treatment. The cases comprised for the most part patients upon whom nephrectomy with or without ureterectomy had been performed for renal tuberculosis; in one there was a tuberculous condition of the adnexa, and in others tuberculosis of other portions of the male or female genito-urinary tract in addition to the renal tuberculosis.

Bacteriology of Chronic Ovaries.—Following out the same line of thought as his well-known investigations into the possible specific bacterial etiology of such conditions as cholecystitis and appendicitis, ROSENOW (*Jour. Am. Med. Assn.*, 1916, lxvi, 1175) has carried out some rather interesting experiments with regard to the causation of certain ovarian conditions. In his previous work, Rosenow claims to have obtained from a number of cases of cholecystitis, appendicitis, etc., organisms which when injected into animals reproduced the same character of lesion, and no other; hence the author's deduction that certain organisms may bear some specific relation to the causation of certain inflammatory conditions of hitherto obscure etiology. While this work has not been definitely confirmed or accepted as yet, it must be considered an extremely interesting attempt to throw some new light on old problems. In studying the possible bacterial etiology of certain ovarian lesions, Rosenow has made cultures from 64 specimens of ovaries removed at operation for the most part because of typical chronic "fibrocystic degeneration;" only a small proportion of the cases gave a history of previous acute pelvic infection, and in only 3 cases was there present a relatively acute process. In a number the history indicated clearly that the pelvic disturbance began after the contraction of a severe cold during the menstrual period or following definite attacks of tonsillitis. The technic used in making the cultures was the same as that employed in the earlier work, shake-cultures from one or more pieces of ovary, at least 1 cm. in diameter, being made in tall columns of ascites-dextrose agar. Of the 3 cases with acute tubo-ovarian abscesses, 2 showed pure cultures of Streptococcus viridans and the third of gonococci. In 10 cases the cultures were sterile. In the remaining 51 cases streptococci were found in 29, only 7 of these showing pure cultures, however. Of the other organisms encountered, Welch bacilli were present in 21 cases, diphtheroid bacilli in 10, a few colonies of Staphylococcus albus in 9, gonococci in 2, colon bacilli in 3, and an aërobic streptothrix in 1. The tubes were cultured in 5 cases, and when positive showed organisms with cultural characteristics similar to those from the ovary. The staphylococci and diphtheroid bacilli are considered by the author as accidental or harmless invaders, whereas the significance of the Welch bacillus is doubtful. It probably, however, plays no determining role in the etiology of fibrocystic ovary. Intravenous injections into animals of 5 of the strains of streptococci showed them to be of a low grade of virulence, rabbits and dogs recovering promptly. Two of these strains appeared to show, however, an elective affinity for the ovary in these animals. The first of these was obtained from a girl, aged eighteen years, with an imperforate vagina, fibrous degeneration of the tubes with closure of the right, and fibrous and cystic degeneration of the ovaries. All cultures from the tube remained sterile, while those from the ovary showed streptococci. A subculture was injected into a female dog, which was chloroformed three weeks later; the ovary showed a number of encapsulated, yellowish nodular areas beneath the capsule, filled with chocolate colored fluid, rich in leukocytes, but sterile on culture. There were no other lesions. The second case was that of a woman, aged thirty years, who developed subsequent to an acute arthritis severe dysmenorrhea and menorrhagia, for which first the left and then the right ovary were removed. Cultures from both showed the Streptococcus viridians; subcultures were injected into 3 dogs and 4 rabbits and the animals killed on the second and third days. All showed severe lesions of one or both ovaries, such as hemorrhages and leukocytic infiltration. Cultures from the ovaries showed streptococci in about half the cases. Five of the animals showed in addition to the ovarian lesions distinct arthritis and other miscellaneous lesions. From these investigations, Rosenow considers the conclusion warranted that fibrocystic degeneration of the ovary, even in the absence of previous acute infection, may be due to a low grade hematogenous infection by streptococci having an elective affinity for these structures. If this be true, it seems possible that the timely eradication of primary foci of infection might in some cases prevent the premature sclerotic degeneration of the ovary.

OTOLOGY

UNDER THE CHARGE OF

CLARENCE J. BLAKE, M.D.,

EMERITUS PROFESSOR OF OTOLOGY IN THE HARVARD MEDICAL SCHOOL, BOSTON.

Supramastoideal Pneumatocele in Chronic Mastoiditis.—O. Muck *Ztschr. f. Ohrenheilk.*, January, 1916). A pneumatocele, in the region entitled, implies a circumscribed space between the periosteum and bone, containing air and extending upward and backward as well as forward from the mastoid surface exteriorly; the result not of injury but of the passage of air from the pneumatic cells of the mastoid, through some defect in the cortical bone, beneath the periosteum elevating it from the bone to varying extent. The author finding no example in the literature of the subject of such a pneumatocele containing the gaseous products of decomposition, reports the following case: The patient, aged four years, had chronic suppurative otitis media of three years' standing; two days previous to examination he had severe pain in the ear, and within twenty-four hours the development of a marked fluctuating swelling behind the auricle extending from 3 to 4 cm. upward and backward. A crescentic incision at the base of the auricle, posteriorly, revealed a decided thickening of the soft tissues and extension of the incision through the periosteum liberated, not pus, but a foul-smelling gas; the scalp was found to be elevated upward and backward, and in the pocket thus formed there were small blood coagula evidently not of recent origin. The cortical surface of the mastoid was pale, without areas of congestion or spontaneous defects. The diploetic interior of the mastoid was, in places, of a light green color without granulomata, the amtabos was in place but the malleus wanting, and there was a large obstructive granulation polyp in the tympanum and a small quantity of greenish-yellow fetid pus in the mastoid cavity. The plastic dressing followed the operation in a fortnight, and the case was entirely healed in seven weeks. There being in this case no spontaneous defects in the mastoid cortex, there being no sutura mastoidea squamosa and no fistulous leakage of pus through the cortex, the only conclusion possible was that the gases engendered in the diploetic spaces of the mastoid had made their way along the normal vascular bone openings outward to the cortical surface and denuded it of its periosteal covering. The preoperative palpation of the postaural swelling, which was apparently provocative of considerable pain, gave the impression of a fluid content.

Otological Report of One Year of Military Service.—OSCAR MAUTHNER (*Monatschr. f. Ohrenheilk.*, December, 1915). The number of cases treated in the ear, nose, and throat department of the Garrison Hospital, No. 6, in Olmutz, in charge of the author, as regimental surgeon, in the first year of the war was 5097, a number equaling that of many polyclinics in time of peace; but the character of the service rendered was essentially different in two respects, and divisible naturally, in two directions, that of estimation of condition and of possible results, as bearing upon capacity for future service, on the one hand, and treatment, on the other, the patients being further divisible into those who came into the hospital because of injuries inflicted by weapons in the hands of an enemy and those whose complaint was the result of the peculiar conditions incident to war. The functions of the department would therefore be: (1) examination, diagnosis and classification; (2) diseases of the ear, including the nose and throat, under conditions incident to war; (3) wounds of the ear, nose, and throat incident to war. Under the first heading came not only the determination of the character of the disease but also an estimation of its degree as bearing upon the serviceableness of the patient, and whether the disease was acquired before or after and during the entrance into service. The number of cases in which there was already existing disease, or in which this had been acquired by other means than that of wounding, proved to be considerable, amounting to somewhat more than 2000 cases, resulting properly from the fact that the acute demand for service had necessitated the calling out of so many men ordinarily beyond service years. The largest number of cases classified as unfit were those suffering from chronic suppurative disease of the middle ear, including nearly 50 per cent. of those patients examined in the ear, nose, and throat department of the hospital and determined unfit for service. Multiplied by the number of military subdepartments carrying on the same work, there is evidence of an unexpectedly large number of men withdrawn from service to the State by this disease. The chronic suppurative disease of the middle ear is in a very large percentage of the cases not only the result of an acute infection, but is distinctly a *morbus paupurum*, and the importance of the increase of institutions in which this disease can be treated and the people taught the necessity of its prevention is distinctly emphasized. Treatment of these cases under the conditions of military service is usually impossible except insofar as operative measures are concerned, and these not infrequently find, and leave, the patient unfitted for return to duty except in some subordinate capacity at the rear. Even when the chronic middle-ear suppuration has come spontaneously to an end, the resultant chronic adhesions and thickening cause an impairment of the hearing in so high a grade as to interfere with the patient's value for active service. Next to the suppurative middle-ear diseases as a cause of unfitness come the results of acute and chronic infectious diseases, foremost among which has been found to be syphilis, 1 per cent. of all the cases unfit for active or secondary service being due to this disease. Of the total examined, including the cases rejected on account of diseases of the nose and the throat, about 60 per cent. of the cases presented at the hospital for examination were declared as fully fit for service. Among the causes of aural complications other than those resulting from wounds, typhus was the most prominent, it having been the author's observation that suppurative inflammation of the middle ear not only occurred frequently in typhus, but that it was often one of the initial symptoms, an observation confirmed by members of the medical staff having charge of epidemic diseases, but contrary to that found in text-books, which placed the complications of the ear in the fourth or fifth weeks of the disease, while in the majority of the cases of this kind under the author's care, by the time the above-mentioned period had been reached, the suppurative middle-ear trouble had become complicated by mastoiditis, demanding operation in 9 cases as compared to 25 operations in cases due to other causes. Diseases of the inner ear and of the auditory nerve were also found to be more common in typhus than in other infectious diseases. Another observation of interest was that of acute inflammation of the middle ear in cholera, intimately presenting the characteristics of a similar manifestation in tuberculosis. A similar middle-ear complication was also observed, but in a much less percentage, in dysentery. The present war has resulted in the publication of a large number of special articles upon injuries to the ear under titles difficult of classification, such as labyrinth vibration, detonation deafness, deafness from hand-grenade concussion, gunshot wound of the skull with cochlear symptoms in contradistinction to which the author gives the results of 200 carefully studied cases, dividing them into two classes, direct and indirect, the direct including those in which the force was applied directly to some portion of the ear, the indirect those in which the effective force was expended outside of the ear and still caused distinctly determinable changes in its condition, this complicated organ consisting of some parts which are directly and others only indirectly attackable, it being understood that this differentiation cannot be maintained in all cases, because under certain conditions there may be no injury to the more exposed portion of the organ of hearing accompanied by a concussion effect producing injury in the deeper seated parts, or the direct attack, in addition to forcible disruption of the exterior portions of the ear, may extend also to the labyrinth and auditory nerve, the protected positions of the more important parts of the organ of hearing being such that the outer ear most frequently, the middle ear but seldom, and the inner ear very rarely, was the subject of direct injury. The majority of injuries to the auricle were those resulting from explosions in the immediate neighborhood and burns resulting from explosions, gases, and flames, as well as those cases in which the injury to the auricle was the result of the exposure to intense cold. These injuries were comparatively slight and the resultant deformity was moderate. There were other cases, however, in which the injury to the auricle was very much more severe, including cuts, burns, tearing away of the upper portion of the auricle, and, in one case, the loss of the greater portion of both auricles. More frequent than the wounding of the auricle were the direct wounds of the external auditory canal and of the mastoid process, gunshot wounds of the mastoid process being repeatedly recurring type, and often found in connection with frontal wounds of the skull, the tympanic cavity being either directly or indirectly injured, and in the majority of the cases the labyrinth subjected only to indirect invasion. In this type of cases the projectile entered either through the external canal or its neighborhood, penetrating the mastoid. In some cases the course of the bullet was in the opposite direction. The result of a simple gunshot fracture of the external canal was usually a membranous and bony narrowing, or even complete closure, of the canal, 10 cases of such absolute bony closure having been observed. The determination as to operation in these cases was based upon the amount of remaining hearing and the presence of a suppurative process behind the bony closure; in the latter cases only was operation determined upon, the preferable operation being that in which the auricle was reflected forward, the radical operation being contraindicated in view of a possible return of the hearing. In 2 of these cases, notwithstanding the fact that the hearing power in both of them was, before operation, determined to be relatively good, neither the drum head nor the ossicles could be found. In 4 other cases in which the wounding of the external canal was accompanied by destructive concussion of the mastoid process the sequestræ were removed in the progress of an antrotomy, the destruction of the bony mastoid being so complete as to have left a portion of the dura bare in one instance and to have included the exit portion of the facial canal in another.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF
MILTON J. ROSENAU, M.D.,
PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,
AND
JOHN F. ANDERSON, M.D.,
FORMERLY DIRECTOR OF THE HYGIENIC LABORATORY, PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Recommendation as to Sanitation Concerning Employees of the Mines on the Rand Made to the Transvaal Chamber of Mines.—W. C. GORGAS (*Jour. Am. Med. Assn.*, 1914, lxii, 1855) reports on his investigations into the cause of the high death rate from pneumonia among the native laborers working in the mines, and recommends measures necessary for the reduction of the death rate and the improvement of the general sanitary condition of the mines and compounds. The death rate of these natives has fallen from 71.7 per thousand in 1902 to 26.84 in 1912; the most prevalent in 1912 being pneumonia, phthisis, meningitis, and enteric fever, their death rates, 9.8, 5.4, 1.3, and 1.1, respectively; but these are much too high as all the employees are men in the prime of life. The death rate from pneumonia is very high among those natives coming from the tropical climate north of latitude 22, being 26.3 for 1912; while a death rate of 8 per thousand among the non-tropicals was comparatively low. A negro having the natural racial low resistance to the pneumococcus, coming from a climate where practically no natural immunity against the disease occurs, and having had but little or no contact with civilization and white man's diseases, into a climate where exposure to cold produces a constitutional depression very favorable for the pneumococcus, is highly susceptible to the disease, especially during the first few months of his employment. These conditions are very similar to those previously existing on the Isthmus of Panama, where the death rate for pneumonia among the black employees of the Canal in 1906 was 18.74 per thousand, which is higher than the existing rate in the Transvaal. In Panama it was found that no particular localities had continuously high rates; the seasonal incidence of the disease was very irregular and inconstant; no difference in the death rates could be determined between the negroes who slept in wet clothes after working in the rain and those who had had a change of clothing; in the barracks the upper bunks were more ventilated and more draughty than the lower, but there is no difference in the mortality of those sleeping above and those below; altitude had but little effect, there being no appreciable difference between the rates in camps at sea level and those at 200 to 300 feet elevation. The only difference in susceptibility was shown to be governed by the length of time the laborer had been on the Isthmus. However, in 1907, the negro laborers were allowed to leave the barracks provided by the commission and scatter out along the line of the canal, build for themselves cabins on the hills, each with a small cultivable piece of land, so that in 1910, 7000 out of 37,000 lived in their separate establishments with their families. Coincident with this scattering of the negroes there was a sudden and permanent drop in the pneumonia death rate on the Isthmus and it was remained low ever since. The death rates for pneumonia for the succeeding years were as follows: 1906, 18.74; 1907, 10.61; 1908, 2.6; 1909, 1.66; 1910, 1.66; 1911, 3.24; 1912, 1.30. During the first few years on the isthmus the negroes were crowded into barracks, allowing each but thirty feet of floor space. Now it is a well recognized fact in military hygiene that overcrowding of the barracks is coincident with inflammation of the upper respiratory passages which at times becomes epidemic. This was the case in Panama and doubtless is the case on the Rand. Thus the non-immunes in close contact with other negroes would develop such inflammation, which would afford the portal of entry for the pneumococcus, resulting in the high mortality. Inoculation against pneumonia as recommended by Sir Almroth Wright has been attempted with varying degrees of success. It is recommended that the Chamber of Mines continue experimental inoculation against pneumonia using different strains of pneumococci and when vaccinating natives that one-half be kept as controls. The common drinking cups and faucets should be abolished not only as a protection against pneumonia but also against tuberculosis and syphilis. The death rate by tuberculosis is very high; in 1912, 5.65 per thousand by pulmonary tuberculosis as compared with less than 1 per thousand for the same year in Panama. Overcrowding plays as important a part in the spread of tuberculosis as in the case of pneumonia. Disinfection in the dwellings of the tuberculous is useful and important, and the disease may be particularly combated by fresh air, sunshine, cleanliness and roomy quarters. Miners' phthisis can be reduced by laying the dust by the more general use of water-sprayers already used in some parts of the Rand. Cerebrospinal meningitis, which at times causes considerable mortality, can be combated by disinfection and scattering. Typhoid fever can be eliminated by the vaccination of all negro employees, and such of the white employees as so desire. The most serious sanitary defect on the Rand is the housing of the native, as he is allowed in general but fourteen feet of floor space, which forces the occupant into close personal contact, largely increasing the spread of any infectious diseases. Scattering and the construction of simple native huts properly laid out, would not only decrease the spread of infectious diseases but would create a native labor force more stable and continued on account of their being allowed to live with their families. The unmarried native should be allowed at least fifty feet of the floor space in the barracks. In regard to the diet of the employees there is room for improvement as the daily ration consists mostly of mealie meal and a small amount of meat, which the native buys himself, and which is too large a proportion of carbohydrates. On the isthmus the best plan was found to be the supplying of a varied diet to the negroes at cost, to be cooked by the family. Sewage systems should replace the bucket system of disposing of night soil, wherever practicable, and in the mines a fly-proof vault system can be employed conveniently and economically. All of the fifty-four mines are each entirely independent as to their sanitation and the care of the sick. Sixty-two hospitals, none of which is equipped or manned in a first class manner, treat 2150 patients. If a combination could be effected a much higher state of efficienty could be brought about at no increase of cost. One or a few larger hospitals would permit a centralization of authority, the best surgical appliances, greater accuracy and uniformity in diagnosis, and better control of all diseases. Finally, the establishment of a central sanitary bureau reasponsible to the Chamber of Mines and entirely independent of the management of the individual mines, the head of this department to represent the mines on all sanitary questions, would result in the efficient supervision and control of all matters pertaining to the health of the employees and the sanitation of the mines.

Intestinal Parasites in Children.—GREIL (*Amer. Jour. Dis. Children,* November, 1915) gives the results of the examination of 665 children for intestinal parasites seen by him in Montgomery, Ala. He found that out of 665, 240 were harboring intestinal parasites or a percentage of 36.1 per cent. The varieties of parasites found were: Hookworms, 177 (62 females, 115 males, or 26.75 per cent.); Hymenolepis nana, 38 (20 females, 18 males, or 5.75 per cent.); Ascaris lumbricoides, 27 (12 females, 14 males, or 4.06 per cent.); Oxyuris vermicularis, 5 (3 females, 2 males, or 0.75 per cent.); Trichocephalus dispar, 5 (2 females, 3 males, or 0.75 per cent.); mixed infections, 2 or more parasites, 12 (6 females, 6 males, or 1.8 per cent.). It is not surprising that hookworm should be found the most common, but the large percentages of Hymenolepis nana, and Ascaris lumbricoides and the small number of Oxyuria vermicularis was somewhat surprising, as the latter has been considered quite common, while the hymenolepis were considered comparatively rare. The author believes that every county and municipality in the south should provide a man for special work along these lines and that children should not be permitted to attend public or private schools until after such examination, and the results prove to be negative.

The Prevention of Pellagra.—GOLDBERGER, WARING, and WILETS (*Public Health Reports,* October 22, 1915), give the results of the observations of the effect of certain dietaries upon the recurrence of pellagra in institutions in southern cities. The dietaries of two orphanages were modified, so that they consisted principally of fresh animal and leguminous protein foods. Since the change in diet, there has not been observed any evidence of the recurrence in any of the 67 persons, who, in 1914, had symptoms of pellagra, nor have any new cases been observed among the pellagrins and residents of 1914, 99 of whom had been under observation for not less than one year. In the second orphanage there has been observed only one single indication of a recognizable evidence of a recurrence among 105 persons who had symptoms of pellagra in 1914, nor have any new cases been observed among 69 non-pellagrin residents who had been under observation for at least one year. At the Georgia State Sanitarium, an institution in which pellagra has been very prevalent, two wards were placed at their disposal, one in the colored female service, and the other for the white female service, in October and December, 1914 for a test of dietaries in a number of pellagrins. The diet in these wards was modified on the same principle as that at the orphanages. The institution routine, hygienic and sanitary conditions were kept unchanged as far as possible to do so. Since the change of diet and up to October 1, 1915, there has not been observed this year any recognizable evidence of the recurrence in any of the pellagrins in these wards, 72 of whom have remained continuously under observation throughout this period, or at least until the completion of the anniversary date of the 1914 attack. During the same period of observation not less than 15 or 47 per cent. of the 32 control female pellagrins have presented recurrences. The authors draw the conclusion that pellagra may be prevented by an appropriate diet, without any alteration in the environment, hygienic or sanitary.

A Milk-borne Paratyphoid Outbreak.—Levine and Eberson (*Jour. Infect. Dis.*, 1916, xviii, 143) report ten cases of supposedly typhoid fever occurred in Ames, Iowa during the early part of November, 1914. The routine diagnostic Widal tests were questionable. A bacteriological study showed that, six to seven weeks after the onset, the sera from the patients tested, were more patent toward B. paratyphosus B than the A type, while B. typhosus was not clumped. Organisms which are indistinguishable from B. paratyphosus, culturally, were isolated from the feces of a carrier suspect, and from the urine of one patient. The occurrence of all the primary cases in a restricted area of the community and on one milk route, the high case incidence among children under fourteen years (70 per cent.); and the location of two possible sources of infection of the milk supply are conclusive that milk was the vehicle of infection. The bacteriological findings indicate that the disease was paratyphoid fever. The outbreak points out the necessity of testing questionable and negative typhoid specimens against the paratyphoid strains.

Insecticides.—Castellani and Jackson (*Jour. Trop. Med.*, November 15, 1915) give the results of experiments carried out in Serbia on the efficacy or worthlessness of substances used as insecticides, and come to the following conclusions: (1) In regard to solid and liquid insecticides, the substances which we have found to be deleterious to body lice (Pediculus corporis de Geer, 1778) are, in the order of their efficiency, kerosene oil, vaseline, guaiacol, anise preparations, iodoform, lysol, cyllin and similar preparations, carbolic acid solution, naphthalene, camphor. Pyrethrum has a very feeble action on lice; while boric acid, sulphur, corrosive sublimate, and zinc sulphate, when used in powder form, have apparently no action whatever. As regards bedbugs, kerosene oil is the best insecticide. Next to it comes guaiacol, one of the most active drugs of those that were tried. (2) Substances which are powerful licecides may have very little or no action upon bedbugs, and *vice versa*. For instance, iodoform which kills lice within ten to fifteen minutes has practically no deleterious action on bedbugs, which may live for more than twenty-four hours when exposed to it. It also has very little effect on fleas. Pyrethrum, on the other hand, has a much more powerful action on bedbugs than on lice. (3) For use against lice on a large scale, as among troops and prisoners, perhaps the best insecticide is naphthalene. This substance has a lower licecide action than kerosene oil, guaiacol, iodoform and anise preparations, such as onethol, but it has a less displeasing odor than the first three named, and is much cheaper than onethol powder. In stored blankets and clothing it is also practicable and of use, as frequently lice are found stored through the summer. Naphthalene is useful also for its well-known deterrent action upon moths. We are speaking here of insecticide powders. As regards liquid insecticides, the American Red Cross Sanitary Commission gave sanction to kerosene by its daily use upon troops and prisoners. (4) For the better class of patients in practice, a menthol powder is to be preferred to naphthalene in most cases, as its odor is not displeasing, while it is repellant to mosquitoes, in addition to mice and fleas. Such powder is especially useful in summer and in hot countries, as it has a cooling effect on the skin and often prevents prickly heat.

Anopheles Punctipennis Say.—Mitzman (*U. S. Public Health Reports*) writes that Anopheles punctipennis say occurs widely in the United States and is found in certain localities where malaria has been investigated. It therefore seems desirable to look more closely into the role of the mosquito as a transmitter of malarial fevers. The only previous work along this line was not considered definite enough to exclude this form as a carrier. An effort was made to make the study as exhaustive as the material would permit although no special attempts were made to simulate the natural conditions. The investigations were limited to subtertian fever and two series of experiments were attempted: one, with recently emerged mosquitoes and a heavily infected carrier undergoing quinin treatment; the other, with older mosquitoes and a lighter human infection, untreated. The anopheles used were bred mosquitoes which emerged August 25–26, 1915. They were kept in lantern chimneys set in deep glass trays, lined with a layer of absorbent cotton, covered with heavy blotting paper and kept constantly saturated with water. A temperature of 21° to 22° C. was maintained. In the first series of experiments, specimens of A. punctipennis were allowed to bite the patient whose blood was examined for the number of gametocytes present among 100 leukocytes. In all he was bitten 664 times and up to the thirty eighth day, the dead or weak mosquitoes were dissected but no infection of the stomach or salivary glands was observed. In the further determination of the possible infectivity of these insects, two healthy persons, whose blood was negative for malaria, permitted these mosquitos to bite them. The mosquitoes were applied from 4 to 180 times but neither person developed malaria. As a control, 14 specimens of A. quadrimaculatus were fed on the same infected person and, as a result, 2 of them showed malarial infection. One of the laboratory force was accidentally bitten by one of these mosquitoes and developed a sharp attack of subtertian fever.

In series 2, older specimens of A. punctipennis, twenty-nine to thirty days, were used to determine if any age difference influenced the susceptibility to plasmoidal infection. The case was one of subtertian malarial fever which had received no treatment and the gametocyte count was taken in this case also. The patient was bitten 158 times by A. punctipennis, 102 times by A. quadrumaculatus, and 6 times by A. crucians. 67 specimens of A. punctipennis were dissected and during a period of thirty-four days, a healthy person was allowed to be bitten 22 times by A. punctipennis. Both of these experiments showed negative results. Out of 60 specimens of A. quadrimaculatus, 8 showed infection and out of 3 of A. crucians, 1 only showed infection.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
JOHN McCRAE, M.D., M.R.C.P.,
LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL; SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL VICTORIA HOSPITAL, MONTREAL,
AND
OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Spontaneous Arteriosclerosis in Dogs.—As greater attention is given to the question of the distribution of arteriosclerosis the more widely disseminated we find it among animals. However, all animals are not equally affected by it, and in some it appears with great frequency at definite periods in their life. The common appearance of medial degenerations in rabbits has frequently been commented upon, while the relative infrequency of its occurrence in guinea-pigs has also been observed. In horses and cattle, medial and intimal disease of the arteries is also quite common in the older animals. Scleroses of the arteries have been reported in monkeys, pigs, sheep, deer and parrots. Although dogs have been quite extensively used in experimental work, they have not been found very favorable in the study of arteriosclerosis. Investigators using young dogs have mainly reported negative results in their attempts to produce arterial lesions. On the other hand, a number of observers have noted the spontaneous development of canine arteriosclerosis. Koellisch found vascular sclerosis in 10 out of 50 working dogs and 13 out of 50 pet dogs. This would suggest that the hard work imposed upon dogs on the continent has no influence in bringing about scleroses of the arteries. STRAUCH (*Ziegler's Beiträge* 1916, lxi, p. 532) examined 56 dogs, 47 being under five years of age and 9 from five to fifteen years. These dogs were of a variety of kinds including lap dogs. Of the animals under five years, there were only

3 showing a mesaortitis and 1 with a small nodular area suggesting early arteriosclerosis. The lesions which he describes as mesaortitis appear to represent a degenerative process. The author draws attention to fine ridges which normally appear in the branches of the aorta and are sometimes mistaken for early scleroses. Of the 9 dogs ranging in age from five to fifteen years, there were evidences of arterial lesions in every one. The aorta was most frequently affected. Arteriosclerosis appeared in the aorta in 7 cases while a mesaortitis appeared in 3. Other large vessels were also occasionally attacked. The scleroses appeared in the intima in the form of diffuse or nodular thickening. The medial degeneration was associated with the laying down of calcium salts. The author was struck by the similarity of the arterial lesions in dogs with those occurring in man. This conclusion appears to be entirely based on the finding of splitting of the internal elastic lamina. A very decided difference from the human sclerosis is the absence of fatty change of either the intima or media.

Atheroma and Other Lesions Produced in Rabbits by Cholesterol Feeding.—Bailey (*Jour. Exper. Med.*, 1916, xxiii, p. 69) carried out an interesting study on feeding egg yolk and cholesterol to rabbits. In many respects his work substantiates the findings reported by others, but also brings out some important features on the disposal of excessive cholesterol in the tissues. The cholesterol and egg yolk were fed to rabbits by mixing them with their daily ration of food. A control animal to which no cholesterol was given but which received large doses of cotton seed oil was also observed. Where cholesterol was fed, cotton seed oil was used as a solvent. The experiments were carried on over a period of from thirty to three hundred and forty-eight days. Eleven of the 15 animals showed definite lesions in both the aorta and pulmonary artery. These consisted of small raised yellowish white spots and streaks close under the inner lining. These spots showed the presence of large cells with fat containing droplets which were anisotrophic. Associated with the accumulation of these cells was a proliferation of fibroblasts and fine elastic fibers. This observation is important in indicating a possible pregnancy of the changes induced. Occasionally a fatty degeneration appeared in the media. He also observed the deposition of fatty materials in the liver. In part this was found in the liver cells as well as in Kupffer cells. This fat also contained cholesterin. He observed cirrhosis in the liver of 6 rabbits. The kidneys of 8 rabbits showed definite macroscopic change. This consisted of yellowish-white streaks arranged radially in the outer zone of the medulla. These streaks were due to a deposit of anisotropic fat within interstitial endothelial cells. These cells appeared to be associated with the lymph spaces. Although some cholesterin fat appeared in the cells of the tubules it was in very small quantities and did not give rise to the macroscopic appearance. The large vessels of the kidney showed but little change in their structure. There appeared to be some relation between scarring of the kidney and the deposit of the cholesterin fat. These scars are similar to those that are not uncommonly found in rabbits. The adrenal was not infrequently found much enlarged. It is probable that the adrenal has some function in the storage and metabolism of the cholesterol. The author believes that the anisotropic fat in the liver produces a cirrhosis.

Immune Reactions against Tumor Growth in Animals with Spontaneous Tumor.—"While the conditions determining the growth of tumors in experimentally inoculated animals has been studied extensively, the conditions underlying the growth of tumors in animals with spontaneous growths are to a great extent unknown. An analysis of these factors in the latter class of animals is of special theoretical and indirectly also of practical interest in as much as such animals correspond to human beings affected by cancer. The investigations are intended as contributions to the analysis of this problem." In thus indicating their problem the authors, FLEISHER and LOEB (*Jour. Med. Research*, 1916, xxxiv, p. 1), compared the rapidity of growth of inoculated tumors in mice already possessing spontaneous tumors with that in normal animals. They also observed the activity of immunity present in normal mice against tumor inoculation to that present in animals with spontaneous tumors as well as the effect upon the spontaneous tumor of the inoculation of another neoplasm. Some interesting conclusions were obtained in this study. It was found that mice with spontaneous tumors do not offer as good a soil for the growth of inoculated tumors as normal controls. The same mechanisms which inhabit tumor growth in normal animals appears in mice with spontaneous tumors. They have further confirmed their previous conclusions that mice with spontaneous tumors are better soil for the ordinary spontaneous but otherwise not readily transplantable tumors than control mice. It was found, however, that those tumors which can be readily transplanted into normal mice also readily take when inoculated into animals with spontaneous tumors. The spontaneous tumors grow best in those animals in which they have originated. This, they believed, was due to a specific condition present in the animal in which the tumor originated, and is not so available in normal mice. After the extirpation of spontaneous tumors, substances which antagonize the growth of an ordinary transplantable tumor were not demonstrated. They believe that spontaneous tumors in contradistinction to transplantable tumors do not produce any considerable quantity of immune substances comparable to those produced by the ordinary transplanted tumor, nor do spontaneous tumors neutralize immune substances produced through the growth of transplantable tumors.

An Experimental Study on Sporotrichosis.—In 1912 D'AGATA (*Lo Sperimentale*, 1915, lxix, 697) isolated the sporotricium Beurmani from a granuloma of the jaw. He was able to isolate the organism in culture and by this means to identify the type. Subsequently he studied the nature of the infection in mice and rats. These animals were inoculated subcutaneously and intraperitoneally. In each he observed the development of granulomatous nodules, and he was able to recover the microorganisms from the lesions. In the peritoneum small nodules were scattered over the surfaces of the various viscera. In the early stages, the tissue reaction consisted of a migration of leukocytes to the infected area followed by an endothelial and fibroblastic proliferation. The central portion subsequently showed necrosis but the leukocytes persisted in and about the necrotic material. The organisms were found in the periphery of the necrosis where many endothelial and giant cells were developed. Fibroblasts were found in the outer zone of the nodule around which lymphoid and plasma cells were also seen. Nodules were also present in the liver, spleen and other organs. These had a similar structure. A full description of the tissue changes is given by the author.

Notes on Certain Anaërobes Isolated from Wounds.—In this study Robertson (*Jour. Path. and Bact.*, 1916, xx, p. 325) obtained cultures from gangrenous wounds received in battle. She was able to isolate a variety of anaërobic bacteria, and classified them according to their reactions on media. Four groups of anaërobes were recognized: (*a*) rauschbrand group; (*b*) perfringens group; (*c*) non-liquefiers of gelatin; (*d*) proteolytic group. The majority of cultures belonging to either the B. perfringens type or the proteolytic type represented by B. malignant edema (Koch). It was not uncommon to have more than one anaërobe in the same wound. Although the author has followed a uniform method for classifying these anaërobes the findings are not conclusive that the grouping can be used in the broad classification of these organisms. In her work she has almost entirely disregarded similar studies made in America.

NOTICE.

Army Medical Corps Examinations.

The Surgeon-General of the Army announces that preliminary examinations for the appointment of First Lieutenants in the Army Medical Corps will be held on July 17, 1916, and August 14, 1916, at points to be hereafter designated. Full information concerning these examinations can be procured upon application to the Surgeon-General, U. S. Army, Washington, D. C. The essential requirements to securing an invitation are that the applicant shall be a citizen of the United States, shall be between twenty-two and thirty years of age, a graduate of a medical school legally authorized to confer the degree of Doctor of Medicine, shall be of good moral character and habits, and shall have had at least one year's hospital training as an interne, after graduation. Applications must be completed and in possession of the Adjutant-General at least three weeks before the date of examination.

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Dr. George Morris Piersol, 1913 Spruce St., Phila., Pa., U. S. A.

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ORIGINAL ARTICLES

THE COINCIDENCE OF LATENT SYPHILIS AND DIABETES.

By Aldred Scott Warthin, Ph.D., M.D.,
PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF MICHIGAN, ANN ARBOR,

AND

Miss Unity F. Wilson,
RESEARCH ASSISTANT IN PATHOLOGY.

(From the Pathological Laboratory of the University of Michigan.)

Very little attention has been given in the literature to a possible relationship between syphilis and diabetes mellitus. Most writers on internal medicine deny any etiological relationship between the two conditions, or do not even mention such a possibility; while a small minority think that syphilis may only rarely be a cause of diabetes or glycosuria. We may here quote Futcher's article on diabetes mellitus in the last edition of Osler's *System*: "In occasional instances diabetes may be traced to a syphilitic infection. Feinberg reported three cases of diabetes and one of glycosuria which he attributed to a syphilitic infection. When syphilis plays a part, the lesion is most probably a local one, and most likely to be situated in the region of the medulla or pituitary gland. Nutritional changes in the brain and pancreas from syphilitic arterial disease must be considered as a possible cause."

On the very next page of Futcher's article there is an apparent contradiction of the above statement as to the occasional relationship of syphilitic infection and diabetes, in the following: "Observers agree in the comparative frequency of glycosuria, or a mild diabetes in *general paresis*. Bond reports having found it in 10 per cent., and Strauss in 9 per cent. of their cases. Glycosuria is an occasional accompaniment of *tabes dorsalis* and *multiple sclerosis*." It is evident that if 9 to 10 per cent. of paretics show glycosuria or a mild diabetes, the relationship between syphilis and glycosuria is not an occasional one. During the last several years there have appeared evidences, more or less vague, that the attention of clinicians was slowly being directed to a more decided appreciation of relationship between the two diseases. The occurrence of positive Wassermanns in some diabetics, apparent improvement following the therapeutic use of mercury or salvarsan, the association of glycosuria in children with congenital syphilis, and the same condition in adults with paresis, tabes and other syphilitic affections are reported in recent literature more or less incidentally. At the meeting of the American Medical Association in San Francisco, I took the opportunity of asking clinicians from all parts of the country as to their experience with coincident diabetes and syphilis, and was surprised to find that the majority of those interrogated thought the coincidence not a rare one. On the other hand, other clinicians with large experience thought the combination of the two conditions to be so infrequent as to be clinically negligible.

Since 1907 there have occurred in the autopsy service of the pathological laboratory of the University of Michigan six autopsies on cases of diabetes mellitus. It is of special interest to record that all six of these cases presented histological changes of syphilis, and that in four of them the spirochetes have been demonstrated in the myocardium, and in one of these cases also found in the pancreatic lesions. The case history of these six cases are briefly as follows:

Case I.—Mr. D. F., aged sixty-two years; American; farmer by occupation. Transferred from surgical clinic to medical February 27, 1907, for diabetes mellitus, gangrene of both feet, and erysipelas of face. No history of venereal disease obtainable. One sister died of diabetes. No other symptoms of diabetes. *Urine*: specific gravity 1030 to 1033; showed marked reduction of Fehling's; 3.2 per cent. Lohnstein; polariscope, 3.3 per cent.; positive acetone. On March 4, patient gradually became comatose, with marked odor of acetone on breath. Died in coma on the next day.

Pathological Findings. The autopsy findings were: diabetes mellitus; emphysematous gangrene; atrophy, fatty infiltration, and chronic interstitial inflammation of pancreas; syphilitic myocarditis and aortitis; orchitis syphilitica fibrosa; atrophy and chronic passive congestion of all organs.

The microscopic examination showed fibroid patches in myocardium, coronary sclerosis, and small perivascular infiltrations throughout the heart wall. The aorta wall showed marked atherosclerosis, with areas of mononuclear infiltration around the vasa vasorum, particularly around the veins of the outer portion of the media and in the adventitia (syphilitic aortitis). The testes showed an old syphilitic orchitis fibrosa. The changes in the pancreas will be described below. This material has not yet been examined for spirochetes.

Case II.—Mrs. M. M., aged forty-five years; American; housewife. Admitted to the University Hospital May 25, 1911. Five months before the patient had first noticed increased thirst and pruritus vulvæ, with increasing general weakness. Mother died at fifty-four years of diabetes; one of patient's sisters also had diabetes; no history of venereal disease; has had two miscarriages; four children living and well. On May 26 developed air hunger and strong odor of acetone. *Urine:* specific gravity, 1026; positive tests for acetone and diacetic acid; glucose, 24.7 gms. per day. Died in coma on May 31.

Pathological Findings. Diabetes mellitus; atrophy and chronic inflammation of pancreas; chronic fibroid myocarditis; syphilitic aortitis; arteriosclerosis; acute parenchymatous nephritis; chronic passive congestion and atrophy of all organs; old syphilis.

The microscopic study confirmed the diagnosis of syphilitic myocarditis, aortitis, and pancreatitis; material not examined for spirochetes. Pancreatic changes will be described below.

Case III.—Mr. J. K., aged thirty-eight years; foreigner; laborer. Admitted October 14, 1913. A few weeks previously began to have excessive thirst and to pass large quantities of water. Lost thirty pounds in four weeks. Has attacks of dyspnea and odor of acetone in breath; became stuporous soon after admission. Admitted gonorrhea; denied syphilis. Died in coma twenty-four hours after admission. *Urine*: specific gravity, 1031; glucose, 154 gms. in twenty-four hours; oxybutyric and acetone tests positive.

Pathological Findings. Diabetes mellitus; chronic interstitial pancreatitis with hyaline fibrosis of islands of Langerhans; fibroid heart; syphilitic aortitis; orchitis fibrosa syphilitica; arteriosclerosis; acute emphysema; passive congestion of all organs.

The microscopic examination showed latent syphilis of heart, aorta, pancreas, and testes. Examination for spirochetes by Levaditi method showed typical spirochetes of syphilis in myocardium, bloodvessel wall in adventitia of aorta and in the pancreas. Pancreatic changes will be described below.

Case IV.—Mr. F. A., aged forty-eight years; American; mail-carrier. Admitted on December 12, 1913. History of alcoholism, but denied venereal infection. One sister died of diabetes. Entered surgical clinic for suppurating wound of right hand. Complained of thirst and was drowsy. Cellulitis of right hand and arm with beginning gangrene. Developed air-hunger on the next day, followed by coma and rather sudden death. *Urine*: specific gravity, 1022; glucose, 40.25 gms. in twenty-four hours; positive acetone.

Pathological Findings. Diabetes mellitus; chronic pancreatitis with hyaline changes in islands of Langerhans; fat necrosis; infected primary squamous-cell carcinoma of finger with purulent lymphangitis of right arm; septicemia; fibroid heart; aortitis; orchitis fibrosa syphilitica; emphysema; early sclerosis; cloudy swelling of kidney and liver; passive congestion of all organs.

Microscopic examination showed chronic syphilitic myocarditis, aortitis, pancreatitis, and orchitis. Spirochetes of syphilis were found in the myocardium in a loose cellular connective tissue bordering upon a fibroid area.

Case V.—Mr. Le F., aged forty years; French; occupation not given. Admitted March 5, 1914. Presented general anasarca, ascites, dyspnea, drowsiness, cyanosis, and deep ulcers on both legs. Left foot had been amputated above the ankle. Remained under observation until death on January 7, 1915. Clinical symptoms those of uremia. Urine tests do not mention glucose examination. Clinical diagnosis: diabetes mellitus; diabetic gangrene; chronic nephritis: myocardial insufficiency.

Pathological Findings. Diabetes; old syphilis; chronic myocarditis; aortitis; hepatitis; pancreatitis; nephritis; orchitis. Chronic passive congestion and atrophy of all organs. Syphilitic ulcers of leg; old amputation; obesity; decubitus; cholelithiasis.

The microscopic examination showed syphilitic myocarditis, aortitis, pancreatitis, orchitis, and gummatous ulcers of legs. Spirochetes of syphilis were demonstrated in the myocardium by the Levaditi method.

Case VI.—Mr. W. E., aged sixty-six years. Entered as an emergency case on January 1, 1915, in a state of coma, moderate fever, auricular fibrillation, rapid irregular pulse, and a spreading cellulitis over the occipital region. Urine gave marked reaction for sugar and definite test for acetone. Complete examination impossible because of patient's condition. Died in delirium on January 3.

Pathological Findings. Diabetes mellitus; phlegmon of scalp and neck; pyemia; metastatic abscesses in lungs, heart, kidneys, and prostate; chronic prostatitis; chronic pancreatitis, with hypertrophy of some islands of Langerhans; chronic fibroid myocarditis; chronic aortitis; chronic orchitis fibrosa; chronic hypertrophic gastritis; old syphilis.

The microscopic examination showed old syphilis of heart, aorta, pancreas, adrenals, and testes. Spirochetes of syphilis were found in the myocardium by the Levaditi method.

Diagnosis of Syphilis. The diagnosis of syphilis in these six cases of diabetes was made upon histological changes alone in Cases I and II, and in the remaining four cases upon both histological changes and the presence of the Spirocheta pallida in the tissues, as shown by the Levaditi method. The material of cases I and II has not yet been studied by the Levaditi method, because of our inability to give the necessary time required for such a research. In Cases III, IV, V and VI the spirochetes were found in the myocardium, and in Case III also in the pancreas, this being the only case in which this organ was examined by the Levaditi method. In Case VI alone were the spirochetes found in large numbers. In all six of the cases the histological changes of chronic fibroid myocarditis and of chronic aortitis of the type always associated with chronic syphilitic infection were present. The microscopic pictures presented by both these conditions are characteristic of syphilis, and would be sufficient in themselves to warrant a diagnosis of syphilis without the corroborating support of the other changes present and the demonstration of the spirochetes. All five of the males showed a typical orchitis fibrosa syphilitica.

Pancreatic Changes. When the pancreas of each of the six cases was given a more detailed study than that made for the autopsy report it was found that the pathological changes were essentially the same in all, but varying in degree. Briefly, these changes may be classified as follows:

1. Atrophy with fatty infiltration (fatty atrophy), involving particularly the tail and body of the organ.

2. Increase of stroma, both inter- and intralobular, particularly marked about the ducts, and extending along the intralobular ducts between the acini and presenting the picture of a chronic interstitial inflammation is shown in all six cases. This is also most marked in the splenic end and body of the organ. The increase of stroma is not uniform but patchy. Normal lobules are side by side with lobules showing a marked fibrosis; and many sections from different blocks may show no increase of stroma at all. Large areas, particularly in the head, appear normal. The lobules showing the increase of stroma are smaller than normal, and contain adipose tissue cells. Occasionally completely fibroid areas are found in the more severe cases.

3. Inflammatory infiltrations, usually small in size, were found in every case, both in the interlobular connective tissue and within the lobules. The cells are almost wholly mononuclears, small and large lymphocytes, and plasma cells. Polynuclears and eosinophiles are rare. The seat of the infiltration is always in a loose, semifluid, proliferating connective tissue, resembling edematous connective tissue, and containing epithelioid fibroblastic cells. These areas are precisely like those in the myocardium containing colonies of spirochetes. In such active inflammatory areas were the spirochetes found in Case III.

4. Changes in the islands of Langerhans were present in all six cases. In all, the islands are undoubtedly greatly diminished in number; in two cases only a few islands remained. Particularly in the tail of the organ is the total or nearly total disappearance of the islands notable. In two cases the remaining islands showed a marked hyaline fibrosis. Opie's hyaline degeneration of the cells of the islands was not seen in any case. The islands are destroyed by a connective-tissue proliferation which soon becomes fibroid and hyaline. A number of hypertrophic islands were seen in one case. No inflammatory infiltrations were found about the islands. It is clear that the destroyed islands are replaced by irregular masses of fibrous tissue showing no remains of the island structure.

5. The acini in all six cases also showed marked changes. In many lobules atrophic acini are present, particularly in those showing marked fibrosis. The majority, however, are larger than normal, this increase in size being very marked in many lobules. The nuclei are larger and the protoplasm shows a marked increase of zymogen granules. Occasionally acini with hyaline protoplasm staining deep red with eosin are found.

6. Numerous structures looking like newly formed islands are found in the areas showing most marked fibrosis and inflammation. At first glance they were interpreted as such. Minute study showed them to be new-formed lobules of acini arising from the ducts. Their origin from the epithelium of the latter can be easily demonstrated. In some cases they have been seen developing inside large dilated ducts. In their earlier stages they very much resemble the islands of Langerhans, because of the small size of their cells, collapsed lumina, and deeply staining nuclei; but centro-acinar cells are found within the undeveloped lumen of the acinus, and they have not the vascular arrangement of the islands. All stages can be traced between these newly formed lobules and large adenoma-like structures with dilated lumina containing centro-acinar cells. They undoubtedly represent regenerative attempts, a new formation of acini from the duct epithelium. In these six cases I have found no positive evidence of any new formation of islands. In one case (Case VI) very large islands were found and were interpreted as hypertrophic.

6. The bloodvessels show in all cases varying degrees of sclerosis.

7. The ducts are often dilated and show thickened walls. Cystic ducts are present in every case, and are probably retention cysts of intralobular ducts due to the fibrosis. In one of these papilliferous growths were seen.

The question that at once arises is: Are these pancreatic changes the result of syphilis, and are they responsible for the diabetes? The very frequent association with diabetes of chronic interstitial pancreatitis, particularly the interacinar (intralobular) type, has been shown by many writers; and this form of pancreatic lesion is generally regarded today as the most common and important pathological finding in this disease. According to Opie[1] "Chronic interacinar (intralobular) pancreatitis which implicates the islands of Langerhans is in almost all cases accompanied by glycosuria." As to the etiology of the interacinar form of pancreatitis, Opie gives *alcohol* and *arteriosclcrosis* as the only definite causes, saying that "in some cases the etiology of interacinar pancreatitis is obscure." He does not even mention the possibility of syphilis as an etiological factor in pancreatitis. In his paragraph on "Syphilis of the Pancreas," he does not mention the occurrence of pancreatitis in acquired syphilis, but says that the pancreas is rarely the seat of gummata occurring as the result of acquired syphilis, and that there are no data with reference to the symptoms or diagnosis of syphilis of the pancreas. In the article on Syphilis by Osler and Churchman[2] the statement is made that the pancreas is only rarely attacked, and that Herxheimer gives only three cases of pancreatic gumma from the literature. Here again the only criterion taken for the presence of a syphilitic lesion is the old one of the gumma, a criterion that no longer suffices for the pathological recognition of syphilitic lesions. On the other side, C. Steinberg[3] says that syphilis leads frequently to interstitial inflammation and induration of the pancreas.

In the six cases of diabetes presented above an interstitial pancreatitis, both interlobular and interacinar, but in all chiefly the latter form, associated with disappearance of the islands, is shown. In all six cases syphilitic lesions are shown in other organs. In one case spirochetes were found in the pancreas itself, making this case positively one of syphilitic pancreatitis associated with diabetes. I think it is reasonable to decide that all six cases have the same etiology.

Are the pancreatic changes the cause of the diabetes, and is syphilis a chief factor in the etiology of diabetes by causing the lesion (interacinar pancreatitis implicating the islands) most commonly associated with diabetes? In order to settle this question the pancreas in each of the other thirty-nine cases of old latent syphilis reported in Warthin's paper on "The Persistence of Active Lesions and Spirochetes in the Tissues of Clinically Inactive or 'Cured' Syphilis" is being studied. A preliminary survey of sections from each of these cases shows that the *pancreas is not normal in a single one of these old cases of syphilis.* In every one a more or less wide-spread interacinar and interlobular (mixed) pancreatitis is found, sometimes in widely scattered areas, in other cases more severe and wide-spread. The essential pathology is the same in all: interacinar and interlobular fibrosis; disappearance of the islands of Langerhans through hyaline fibrosis; atrophy, compensatory hypertrophy, and regenerative new formation of acini; localized lymphocyte and plasma-cell infiltration. Hypertrophic islands are found, but no newly formed ones. The severity of these changes varies greatly in different cases and in different parts of the same organ. The process is essentially a *patchy* one, except in the most severe cases, when it may involve the greater part of the gland. The tail and body of the organ are always more involved than the head.

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[1] Osler's System.

[2] Ibid.

[3] Aschoff's Pathologische Anatomie, Band ii.

In the 41 cases of latent syphilis already reported there were six cases that showed on preliminary study very marked changes in the pancreas. Two of these were the two cases of diabetes, Cases III and IV, of this paper. The other four cases had no clinical history of diabetes or glycosuria. It is possible that they might have had it without symptoms, so that it was not discovered clinically, as the patients were all over forty years of age. It does not seem probable, however, that it was missed. As far as it is possible to tell without sectioning the greater part of the organ, the pancreatic changes in these four non-diabetic syphilitics are precisely the same and apparently as marked as in the diabetic cases. On going over our autopsy slides for a number of years back and examining slides of pancreas from our syphilitic cases a number of non-diabetic cases were found presenting similar marked interacinar pancreatitis. It would seem, therefore, that if the degree of change is not the factor responsible for the diabetic symptoms there must be some other explanation of the latter. Possibly associated changes in liver, adrenals, hypophysis, etc., may be necessary to produce the diabetes phenomena. If this is true we have no knowledge of such changes at this time. In the meantime we are making a comprehensive study of the pancreatic changes associated with syphilis, and shall make a full report of these later.

CONCLUSION. Our material shows that a combined interlobular and interacinar type of pancreatitis with loss of the islands of Langerhans is extremely frequently associated with old latent syphilis (practically all of our cases). That in the great majority of cases the pancreatitis is localized and patchy in character, and more rarely severe and diffuse. That diabetes may be associated with the more marked degrees of syphilitic pancreatitis; and in our autopsy service all of our diabetes cases have been so associated; but that a number of cases of syphilitic pancreatitis of similar degree of severity have not presented the clinical symptoms of diabetes. It seems very probable, therefore, that *latent syphilis is the chief factor in the production of the form of pancreatitis most frequently associated with diabetes, but that diabetes is not always coincident with severe degrees of this type of pancreatitis.*

DERMOIDS OF THE MEDIASTINUM.

By Arthur E. Hertzler, M.D.
KANSAS CITY, MISSOURI.

The occurrence of mediastinal dermoids is infrequent, there having been but 72 cases reported in the literature. Rare as they are, however, when they are encountered the fate of the patient is largely dependent upon the surgeon's knowledge of their peculiarities. Inasmuch as such knowledge is dependent upon a familiarity of recorded cases, a tabulation of cases heretofore observed seems worth while.

The case reports collected from the literature, herewith appended, are many of them deficient in detail, yet they all contain some point of interest and are all included in this list, to which I am able to add one case of my own.

From these reports, one is able to formulate a fairly comprehensive life history of these tumors and to gain a fairly clear notion as to the symptom-complex that should suggest their presence. Though most of the tumors were first noted postmortem, a sufficient number have been subjected to operative treatment to furnish some idea of the line of procedure best adopted in the individual case.

My case is as follows: Mrs. W., aged twenty-three years; has always enjoyed good health. In November, 1914, she noticed some difficulty in respiration and had some sense of fulness in the neck. Soon afterward a bulging was noticed above the breast bone. She consulted several surgeons, who made a diagnosis of mediastinal sarcoma and refused treatment.

At examination a bulging in the suprasternal notch was apparent on inspection. The skin covering this area was slightly reddened. On palpation the tumor was slightly tender to touch and presented a soft semifluctuating resistance. The mass extended 2 cm. above the upper border of the sternum and was hidden by the sternomastoid muscles on either side. There was no bulging of the sternum or of the costal cartilages. On percussion there was dulness extending on either side of the sternal borders and downward as far as the angle.

Because of the reddened skin and boggy feel of that portion of the tumor accessible to palpation the diagnosis of dermoid was suggested, because of the close resemblance to the appearance and and consistency of irritated wens. This opinion was strengthened by the globular outline of the substernal dulness. Sarcoma was excluded because of the consistency of the palpable portion of the tumor and because only the upper portion of the mediastinal space was occupied by the tumor.

Operation was begun by exposing the upper portion of the mediastinum. A transverse incision was made over the upper border of the sternum, extending well beyond the insertion of the sternomastoid muscle on the left side. The insertion of the muscle was severed. The superior pole of the globular tumor was thus readily exposed. This was freely incised and a grayish-yellow greasy fluid escaped. After this was sponged out a mass the size of a walnut presented. This was covered with fine lanugo-like hair of the color of a newly hatched goslin. The appearance of this mass established the diagnosis without question.

The operation was completed by the removal of the mass and the exsection of as much as possible of the sac. The part adjacent to the sternum was readily removed; that of the lateral borders caused greater apprehension. The posterior wall of the cyst was in close apposition with the large vessels of the neck, and was allowed to remain. The cavity was swabbed out with iodin and the wound was closed except for a small opening admitting a drain. This was removed in a week and the wound rapidly became closed, and has remained so.

The mass removed presented a dermal surface studded with the fine hair above noted. On section the mass showed a fatty tissue, save for the epidermal covering. On microscopic examination stratified squamous epithelium and sweat and sudoriferous glands with hair follicles were noted.

The cyst wall was of the same structure, save that hair was much less abundant and the glands sparse. There were no more highly organized tissues present.

Age. The majority of the cases have been observed in early adult life, the largest number being noted between the ages of twenty and thirty. The extremes of life are not exempt, one case having occurred in infancy, and another at four and one-half years, and other instances have been recorded in which the disturbance has been delayed until advanced age. By decades the cases in which the ages are given are as follows:

Before ten: males, none; females, 4 cases. Between ten and twenty: males, 4 cases; females, 4 cases. Between twenty and thirty: males, 10 cases; females, 13 cases. Between thirty and forty: males, 7 cases; females, 5 cases. Between forty and fifty: males, 8 cases; females, none. After fifty: males, 2 cases; females, 5 cases.

Sex. The sex of patients is about evenly divided. The totals of these records are as follows: males, 29; females, 32.

Symptoms. The premonitory symptoms are of two groups, those due to pressure and those due to irritation of the environment by the epidermoidal contents. The most frequent symptom was due to encroachment upon the environment by the expanding tumor.

Pressure Symptoms. These are most frequently manifested by cough and dyspnea, less often as pain from pressure. This symptom was present in 28 cases. Cough when due to pressure is caused by irritation of the nerves. Cough of another type was caused by irritation of the bronchi when perforation was impending. When due to irritation the character of the cough is similar to that noted in pressure from aneurysm. A single case of cord paralysis has been noted.

Dyspnea, noted in 23 cases, seems to have been due to direct pressure on the trachea or bronchi, or from pressure upon and displacement of the lungs. In 3 instances death has occurred in dyspneic attacks. Dysphagia was present in 3 cases (52a, 59, 60)[1].

Irritation from the Tumor. When from causes usually unknown the tumor becomes the source of reactive inflammation, phenomena of a more violent character are induced. The cause for this irritation is not clear. The gradually increasing amount of the cyst contents probably undergoes some chemical change which inflames the sac and irritates the environment. In this they imitate the life history of wens. This similarity of reaction to that so often noted in wens was the condition that suggested the diagnosis in my patient. Pleurisy has often been diagnosed in such instances, and often exudation about the tumor has resulted which gave rise to the diagnosis of pneumonia. Often the tumor has been accidentally encountered when supposedly pleural exudates have been attacked surgically. When the bronchi are irritated, perforation into them during attacks of coughing has been noted in three cases. The attendant expectoration of other grumous material and hair has led to a positive diagnosis more often than any other factor. The invasion of the bronchus by the tumor seems to be in the nature of a pressure necrosis, often enhanced by a secondary infection of the tumor contents. The irritation of the bronchus is responded to by the production of glassy mucus. After perforation, honey-like fluid, atheromatous material, and hairs have often been observed. Clubbing of the fingers (63) and fingers and toes (57) have been noted.

Relation to Environment. The greatest possible variation in their topographical relations have been noted in dermoids of the mediastinum. The typical location of the simple dermoid is represented by my own case, a sac occupying the space between the sternum, great vessels, pericardium, and soft tissues covering the episternal notch. Every possible variation has been reported. One existed as a small egg-sized cyst in the upper part of the lung (33) near the hylus (7), while others occupied the mediastinal space and projected boldly out into the pleural cavity, and some extended from the sternum to the diaphragm, markedly displacing the lung.

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[1] Figures in parentheses refer to references in the bibliography at end of article.

In one instance a retrosternal dermoid communicated by a small sinus with a similar tumor external to the sternum (39).

The relation to the surrounding structures is the factor that decides the treatment possible. For this reason these various points of attachment are worthy of note.

Connected with a bronchus, 7 cases (2, 6, 33, 36, 37, 38, 46).

Adherent to pericardium or pleura, 12 cases (7, 14, 20, 21, 26, 38, 41, 52, 63, 64, 67, 68).

Attached to lung or protruding into them, 9 cases (7, 10, 16, 19, 23, 24, 28, 45, 67).

Attached to the diaphragm. 11 cases (3, 8, 10, 22, 24, 32, 34, 41, 42, 45, 64).

Attached to the large vessels, 4 cases (1, 5, 31, 69).

Adherent to chest wall, 1 case (3).

Eleven cases extended into a lobe of a lung (6, 14, 16, 27, 33, 36, 37, 44, 47, 57, 58).

STRUCTURE. Two types may be distinguished, those in which epidermoidal tissue alone is present (28 cases) and those in which tissues from two or more of the germ layers are in evidence (25 cases).

The Simple Epidermoidal Type. These are usually a simple cyst or, at most, a conglomeration of cysts the lining of which is covered with stratified epithelium, with hair follicles, and with sweat and sebaceous glands; but a few cysts have been noted in which all appendages have been absent. Some of the simpler cysts have compartments lined with columnar epithelium, with or without cilia. The contents of cysts is usually formed by cells, fatty material, and hair. The material when in a recent state may be honey-like. A frequent striking accompaniment of this type is polypoid excrescences which project into the cavity of the cyst. These are covered with the same epidermoidal elements which line the cyst. In my case such a mass presented at once ofter the cyst was opened. Instead of or associated with such masses may be ridges of more solid tissue which traverse the cysts, dividing them partially into compartments. The mass of the projections are formed of fat.

The Teratoid Type. In the more complicated type, in addition to the epidermoidal elements, cartilage and bone are frequently found. Less often teeth have been noted. Glands, supposedly from the gut tract and from the thyroid, have been recorded. Non-striated muscle cells have been observed.

In many instances polypoid excrescences, as already noted for the simple type, project into the lumen of the tumor. These are fatty masses covered with epidermis containing fine hair, as in the simple type, but may also contain other elements. Teeth have been noted at the base of these in 6 cases (1, 32, 36, 37, 39, 42). These excrescences may form in numbers of two to six or more, and vary in size from 1 cm. square to tumors the size of a small apple.

In some of the simple epidermoid type, cuboidal or columnar epithelium is found. It is possible that these should be classified with the more complex tumors. Christian makes the suggestion that these cells may be derived from the stratum Malpighii, within which the desquamation of the other layers has occurred. The structure of these cysts recalls the structure of thymic cysts, and it is possible that this is really their relationship.

Genesis. The origin of dermoid and teratoid tumors of the mediastinum is closely associated with the development of the thymus and thyroid glands. The close relation between the ectodermal and entodermal elements in the neck has been pointed out by Minot. That mediastinal dermoids have their origin in the upper part of the sternum is evident from their topography. Even those tumors which exhibit their greater bulk in the lower thorax retain attachments high under the sternum. In some of the reported cases, bands have extended up as far as the thyroid, suggesting an even higher origin. The existence of intestinal epithelium, as reported in one case (67), would seem greatly to complicate the problem. However, the reports are so lacking in detail that the possibility that the glandular structures observed may bear a relation to thyroid and thymus tissue (17, 20) suggests itself. Salivary gland tissue was observed in one case (68). The frequency of complicated tumors in the salivary glands is worthy of note in this connection. The association of the mixed tumors of the salivary glands and the thymic cysts would present all the elements that have been within certainty observed in mediastinal dermoids, save the teeth. The presence of teeth seems to present a barrier to a plausible explanation for the origin of the tumors under discussion, and compels us to fall back on the generalities usually employed in explaining the origin of epidermoidal or teratoid tumors in other parts of the body. Bergmann's case (39), in which a part of the tumor lay anterior to the sternum, suggests strongly that the tumor arose from a disturbance at the time of the closure of the anterior chest wall. A satisfactory explanation for the topographical relations of the more complicated type has not been presented.

Diagnosis. The presence of mediastinal tumor is most often suggested by the symptoms previously noted.

Except in a few instances their size has been such as to give the usual definite physical signs of mediastinal solid bodies. In 8 instances this dulness extended lateral to the borders of the sternum, and in 9 instances it extended above the upper border of the sternum, or above either or both clavicles. In a number of instances the dulness extended over much of the side of the chest, reaching the lateral wall usually at or below the angle of the scapula. The extent and direction of the dulness above indicated presents a strongly presumptive diagnostic sign. This is made doubly so if there is a bulging above the sternum or clavicle. This had, in my case, the boggy feel of a wen, which was quite suggestive.

The examination of the sputum has given positive results in 8 cases by the discovery of hair (2, 6, 9, 27, 38, 44, 58, 66). The presence of fat or a glycerin-like fluid and squamous epithelium is strongly suggestive. The absence of pus cells may differentiate it from a simple abscess, and a negative search for tubercle bacilli is significant. In several cases aspiration has produced diagnostic evidence. Hair has been obtained by this means and presents positive evidence. Squamous keratinized cells undergoing fatty degeneration is equally positive, and fatty material, which is undergoing decomposition (13), is almost equally so. When incised the escape of honey-like material with flaky debris is strongly suggestive, as in my case. The ridges and polypoid masses covered with fine hair are readily recognizable when seen for the first time.

Differential Diagnosis. *Aneurysm.* Those confined to the retrosternal space or that immediately adjoining will suggest the more frequent aneurysm. The absence of beats or pulsation are the signs to be relied upon. The presence or absence of the Wassermann reaction may be of some value. Frequently the early age of the individual is of importance.

Tuberculosis. In a few instances tuberculosis has been diagnosed, owing to the dulness in the upper part of the lungs associated with expectoration. The absence of bacilli should be enough to warrant care in making such a diagnosis. Tuberculosis existed as a complication in 5 cases (6, 29, 33, 44, 57).

Empyema. The history of pain and dyspnea with the presence of fluid in the lower chest has led to error in diagnosis. Examination of the contents obtained by aspiration should be distinctive. In those rare instances in which there is a pleural exudate associated with the intrapulmonary dermoid and only the contents of the former is obtained at aspiration, error is very likely, and the operator may consider himself fortunate if he orientates himself during the course of the operation.

Malignant Tumors. The malignant tumors which are primary in the mediastinum usually run their course rapidly in contradistinction to the long history of the dermoids. However, if a dermoid becomes infected the increase in size may be even more rapid than in malignant tumors. Nevertheless, some of the dermoids have presented such urgent problems that a history was not available. Though the roentgen rays have been employed in but a few cases of mediastinal dermoids it is quite possible that the irregular masses of mediastinal malignancies might be distinguished from the more sacular dermoids. If the latter contained calcareous material, teeth or other bony structures diagnosis might be aided.

Benign Tumors. Lipomas and tumors of the thymus have presented pictures that might have been confused with mediastinal dermoids. In such cases aspiration or diagnostic incision alone could present a positive answer. With perfected technic it is to be hoped that more frequent diagnostic operations will be undertaken.

Prognosis. The discussion of the prognosis is in a great measure anticipated by the natural history of the disease. Those instances in which the disease has been spontaneously fatal, hemorrhage (7.45) and dyspnea (23, 28) have been the most common causes. The size and situation, together with the reactive changes which take place in the tumor, are the determining cause. Except in very small tumors in favorable situations it is safe to say that the patient's life will be jeopardized sooner or later unless the tumor is removed or its development curtailed.

Malignant degeneration has been noted in 4 cases, carcinoma in one (69), and sarcoma in three (52b, 32, 12).

Duration. The duration as manifested by the symptoms has varied from very brief periods to the natural life of the individual. In most instances the duration has been from one to four years. In one instance the patient died in dyspnea and no history was obtainable. In others the lesion was discovered in patients who died of some other diesase. In a number there has been a disturbance of a varied and intermittent character during the entire life of the individual.

Treatment. Obviously, surgical treatment alone can be of avail. Of the 27 cases operated on there was recovery in 5 (31, 39, 40, 50a, 51), improvement in 13 (13, 18, 24, 25, 29, 34, 35, 43, 48, 49, 50, 56, 57), in 4 the result was indeterminate or not stated (11, 41, 42, 63), and 5 died as the direct result of the operation (52, 53, 61, 67, 68). In most of the cases incision and drainage with the excision of the polypoid masses has been the treatment employed. In those cases reported as improved this was employed which resulted in a lessening of the size of the sac, leaving a more or less annoying sinus. A few were permanently cured by this simple means.

Total extirpation would be the ideal treatment. This was accomplished by Bastianelli (31) at a secondary operation. Total excision has been strongly recommended by von Eiselberg (52). In his 3 cases the loss of 1 by secondary hemorrhage and another by pericarditis is sufficient to show that even in the most skilled hands total removal is attended by too great a mortality to warrant the attempt at total extirpation. In many cases the relation of the tumor to surrounding structures is such that total extirpation is anatomically out of the question.

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THE RELIEF OF CHRONIC OBSTRUCTIVE JAUNDICE BY PALLIATIVE OPERATIONS.[1]

By John F. Erdmann, M.D.,
PROFESSOR OF SURGERY AT NEW YORK POSTGRADUATE MEDICAL SCHOOL AND HOSPITAL,

AND

Chas. Gordon Heyd, M.D.,
ADJUNCT PROFESSOR OF SURGERY AT NEW YORK POSTGRADUATE MEDICAL SCHOOL AND HOSPITAL.

The object of this paper is to review the literature pertaining to obstructive jaundice and to offer some suggestions for the operative relief of chronic cholemia. We will consider only those cases of biliary and pancreatic obstruction, with or without duodenal involvement, which are incident to malignant disease or irremovable tumors about the terminal portion of the common and pancreatic ducts. Since persistent and increasing jaundice is in the large majority of cases due to malignant disease we will outline what can be done in the way of palliation for the unfortunate patient suffering from malignant icterus.

The clinical picture of chronic obstructive jaundice is so well recognized as to call forth little comment. However, the rapid loss of weight, the emaciation and asthenia, the pruritus and disturbing mental states incidental to cholemia very often render imperative the attempts at operative relief.

A consideration of the mechanical factors involved in organic occlusion outside of the common duct, but within the head of the pancreas or intrinsic involvement of the duodenal segment at or beyond the ampulla of Vater, enables one to establish certain procedures best indicated for relief. It follows that relief of biliary stasis must be provided by a drainage operation between some portion of the biliary apparatus and the gastro-intestinal tract.

The indications for operation in malignant obstruction to the biliary flow may be summarized as follows: (1) Mistaken diagnosis —not infrequently one operates for supposed malignancy and finds the diagnosis has been incorrect and by the institution of drainage the inflammatory condition subsides with recovery of the patient. It is only upon such premises that the occasional "cures" can be reasonably explained. "No one living is infallible in the differential diagnosis of obstructive jaundice. The diagnosis is always so difficult and the chance of a life saved is so important that however positive the evidence of malignancy may be I now advise operation in all cases." (Moynihan.) (2) The relief of distention pain—all cases do not suffer from pruritus or the mental states of cholemia but suffer a gradual increasing pain from distention of the biliary apparatus. (3) Intractable pruritus, in many cases so severe that the patients positively demand relief. (4) Social—to prolong life in comparative comfort; to give the patient relief from his jaundice so that he may live with his family until such time as death takes place from metastasis or local extension of the growth. (5) Surgical euthanasia. The primary operative mortality in these conditions will be high, but considering the absolutely hopeless outlook, together with the urgent demand for relief, one is warranted in selecting an operative procedure entailing a high rate of mortality.

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A neoplasm at the ampulla of Vater either by its presence, by kinking of the duct, or associated edema of the mucous membrane of the duodenum or common duct will bring about not only biliary obstruction but a variable degree of pancreatic obstruction. The degree of obstruction to pancreatic secretion will depend upon the individual anatomical topography of the ducts of the pancreas. In about 83 per cent. the duct of Wirsung carries the entire pancreatic secretion. In about 12 per cent., however, the duct of Santorini is the main duct, while in 54 per cent. the duct of Santorini may act as a substitute for the duct of Wirsung. In certain cases the duct of Santorini might remain uninvolved for a considerable period of time, and, moreover, the duct of Santorini is not infrequently connected with the duct of Wirsung, and thus it is possible for a drainage of the pancreatic secretion to take place into the duodenum even with almost complete biliary stasis; in fact, there may be complete biliary stasis with little or no pancreatic retention. Certainly, this must be an extremely rare condition, and, aside from its theoretical interest, does not possess any particular technical importance over the general run of cases. Cholecystenterostomy will deliver the biliary secretion or excretion into the intestinal tract. The stools would contain bile and would present an approach to normal coloration, and there would be a cessation of the jaundice and an absence of bile in the urine. This operation, however, could only rarely affect the pancreatic secretion, and the few cases that it did influence, pancreatic drainage would depend upon retrograde flow of pancreatic juice into the common duct, then through the cystic duct and gall-bladder into the intestinal tract. In the large majority of cases the patients suffer from a lack of pancreatic secretion in the intestine with a corresponding lack of pancreatic digestion, as evidenced by the bulky frequent stools, showing the increase in the total amount of fats and the changed relationship between unsaponified and saponified fats and the absence of adequate proteid digestion. Therefore, in spite of the elimination of jaundice and the biliary stasis by cholecystenterostomy, any or all of these cases may proceed to a more or less rapid death as the result of pancreatic insufficiency.

Any chronic obstructive condition of the duodenum below the ampulla of Vater will introduce in addition to the signs of biliary stasis those of pyloric stenosis, and in two of the cases presented herewith the clinical picture was that of chronic pyloric stenosis and chronic obstructive jaundice. (Cases I and II.) In Case I there was a distinct interim between the syndrome of pyloric obstruction and a second syndrome of biliary stasis. In this particular case a malignant ulcer existed, perhaps primarily, of the duodenum below the ampulla of Vater, and for which a posterior gastro-enterostomy had been performed. Subsequently, the ulcer more thoroughly invaded the ampulla and brought about biliary obstruction, for which a cholecystenterostomy was performed.

In obstructive conditions at the ampulla of Vater it is usual to find the gall-bladder distended with bile. (Courvoisier.) This is not necessarily always the case, as a distinct hydrops and a well-dilated common duct filled with clear mucoid fluid has been observed, and when this rather uncommon condition is seen it is associated with patulous cystic and hepatic ducts and mechanically represents a pressure acholia. Kausch (quoted by Outerbridge) made a careful study of such a case: "At operation upon a patient with steadily increasing jaundice the gall-bladder and common duct were found enormously distended with clear fluid; a cholecystostomy was performed and for two hours clear fluid flowed from the tube. Then the discharge began to be slightly colored, and by the end of six hours it had assumed the appearance of somewhat pale bile, large quantities of which continued to flow as long as the sinus was left open. At autopsy, some weeks later, a small tumor was found at the papilla of Vater. Kausch thinks that the hydrops in these cases is due to excessive secretion by the mucosa of the gall-bladder and ducts, whereby the duodenal opening being occluded the pressure in the biliary system being so raised that the bile secreted by the liver cells is poured not into the excretory ducts but back into the blood and lymph vessels of the liver." This condition, hydrops with cancer of the pancreas, was found in Case VII. When the mucoid material drained away, bile was obtained through the drainage tube.

The most frequent obstructive condition is from carcinoma of the pancreas, ampulla, or duodenum. Cancer of the duodenum represents about 0.4 per cent. of all carcinomata, and at least 70 per cent. of this number are carcinoma of the ampulla of Vater. (Geiser). Pancreatic cancer is the most rapidly fatal of any form of carcinoma; death ensues within seven or eight months from the time of onset of noticeable symptoms, and occurs usually before the growth metastasises or obtains any great local extension. "There is probably no position within the body, outside the central nervous system, where a growth, while yet so small, is heralded by more wide-spread symptoms than at the lower end of the common bile duct." (Upcott, p. 717.)

Up to date about 22 reported cases of excision of growths at the ampulla have been reported and the results are not encouraging; 8 primary deaths and 5 subsequent deaths. Of the 5 surviving any length of time, 2 were well at seven months, 1 ten months, 1 two years, and 1 three and three-quarter years after operation.

Under most circumstances any operative intervention will be in the nature of a palliative procedure to provide drainage for the biliary secretion or excretion. Given an obstructive condition to the common duct or its terminus, the ampulla of Vater, we have a choice of a variety of operations. The simplest is external drainage by means of a cholecystostomy. Such an operation entails a rapid loss of bile salts and body fluids and should not be the procedure of choice, but an anastomosis between the gall-bladder and some nearly approximate portion of the gut tube is physiologically and anatomically correct. Theoretically an anastomosis can be made between the gall-bladder or the hepatic duct or the common duct and any contiguous bowel surface as (1) an anastomosis of the gall-bladder and varying portions of the gastro-intestinal tract—cholecystogastrostomy, cholecystoduodenostomy, cholecystenterostomy, cholecystocolostomy; (2) anastomosis between the hepatic duct and certain portions of the viscera, preferably the stomach or duodenum or a portion of the small intestine; or anastomosis between the common duct and the stomach, duodenum, or small intestine.

The choice of a particular operation will depend upon a number of factors such as (1) the physiological efficiency of the procedure; (2) the ease of technical accomplishment; (3) the relative immunity from ascending infection; and (4) the immediate and remote effect upon the patient's metabolism. The classical operation of cholecystoduodenostomy will more nearly simulate the natural condition of biliary drainage than any type of operation. Yet the mortality of cholecystoduodenostomy is certainly greater than cholecystogastrostomy. Moynihan anastomosed the gall-bladder to the stomach in 21 cases; 20 patients recovered from the operation and lived for several months or years without suffering any disability which could be attributed to the entrance of bile into the stomach.[2]

In practice the biliary portion usually found most convenient is the gall-bladder. A consideration of the merits of cholecystogastrostomy, cholecystenterostomy, and cholecystocolostomy seems to prove that the best results are obtained with the first procedure. Physiologically considered there is no objection to the presence of bile in the stomach, as has been demonstrated so often clinically[3] and proved by Strendel in his experiments on animals. Technically, the union of the gall-bladder and the stomach is probably more easily performed than any other form of anastomosis, as the parts are naturally in close and intimate relationship, and little if any mobilization is necessary to bring the viscera in apposition. Cholecystenterostomy carries with it the possibilities of angulation and the necessity for a secondary entero-enterostomy to prevent kinking and of course increased risk. On theoretical grounds the union between the colon and gall-bladder is to be deprecated, and physiologically it is defective as it empties the biliary secretion into a portion of the gut tube not given to digestive processes; and upon other grounds it is also objectionable. (1) On account of the reflux of the highly charged bacterial content of the colon, and (2) the possibility of reversed mucous currents as described by Bond; (3) the loss of the digestive functions of the bile, especially in the saponification of fats; (4) the fact that the bile is so soon evacuated with the stool means a rapid loss of the acid salts of the bile which would normally be reabsorbed in the intestine. However, it is a rather peculiar observation that in spite of these manifest defects, in this series the cholecystocolostomies had a longer period of postoperative longevity than any of the other cases up to 1914.

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[2] Moyniham, ii, 335.

In a fairly large experience with pancreatic disease we have observed in a few cases a peculiar clinical picture that occurs about thirty-six hours after operation. The patient reacts well up to this time and is apparently progressing nicely. Then within the following four to six hours there is a rapid fall in blood-pressure, cold clammy perspiration, and a diminished quantity of urine showing acetone and diacetic acid. By means of continuous proctoclysis and saline infusion, urinary elimination is increased and correspondingly the patient improves. Some of the deaths that occur after operation in cases of chronic jaundice probably have an element of acidosis in their termination. It is possible, experimentally, to produce a well-defined acidosis in obstructive jaundice. It is a matter of great interest to know how important, as a death-producing factor, is the retention of beta-oxybutyric acid and its derivatives in this class of cases.

Carcinoma of the duodenum and papilla of Vater; cholecystostomy and posterior gastroenterostomy; secondary operation; cholecystojejunostomy; recovery.

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[3] In a paper, Surgery of the Gall-bladder and Ducts, Medical News, March 26, 1904, by Dr. John F. Erdmann, attention was called to the clinical use of powdered ox-gall. "When drainage has been done, flatulency with distention chiefly limited to the epigastric and umbilical region is a depressing feature. This is readily remedied by the use of 5 to 10 grains of powdered ox-gall every four hours, continued from two to four days."

Case I.—J. S. (service of Dr. Erdmann), machinist, aged forty-six years. Entered the Post-Graduate Hospital on December 30, 1912, complaining of pain and vomiting after meals. Duration three months. His illness began three months previous to his admittance to the hospital with pain in the epigastrium followed in from a few minutes to a few hours by vomiting. The pain was of a colicky character, more or less localized in the upper median line and always induced or made worse by eating and always relieved by vomiting. Vomiting occurred only after the development of pain and then usually once or rarely twice. No blood had ever been noticed in the vomitus which consisted of previously ingested food mixed with mucus and occasionally with a large quantity of greenish material. For the last month the pain has been progressively worse and occurred immediately after eating, and was always relieved by vomiting. Patient lost twenty pounds in weight since the onset of the present trouble. There has never been any history of jaundice and no gastric trouble up to three months ago.

An examination of the blood showed 9100 leukocytes, with 76 per cent. polynuclears and 24 per cent. lymphocytes. The urinary examination and the Wassermann were negative. An analysis of the gastric contents showed considerable retention, with a total volume of 275 c.c.; free hydrochloric acid, 19; combined, 9; total acidity, 36; no blood. The fluoroscopic examination made by Dr. Kast showed evidence of marked gastric retention, and an obstruction of some kind, probably a tumor of the duodenum the first portion of which was markedly dilated, with the hepatic flexure drawn up between the duodenum and the median line. From the fluoroscopic findings Dr. Kast made a diagnosis of stenosis of the midportion of the duodenum.

Operation, January 14, 1913, revealed a marked dilatation of the pylorus and the first portion of the duodenum, with an annular constriction of the duodenum at the ampulla of Vater. The gall-bladder was greatly dilated and contained considerable fine biliary sand. A cholecystostomy and posterior gastro-enterostomy were done and the patient left the hospital twenty-one days later, February 4, 1913, apparently well.

Postoperative History. The patient returned home and continued to gain in weight. About two weeks later he became jaundiced with the development of pain in the right upper quadrant. In a few days the wound reopened and discharged considerable bile and mucus. The patient was readmitted to the hospital on April 9, complaining of jaundice, vomiting, and inability to retain food. Temperature, 101°; pulse, 132; respirations, 28. On April 11, 1913, the abdominal wound was reopened and it was found that the tumor, which had constricted the duodenum, had become mushroom-like in its growth and about three times its original size, inducing complete biliary obstruction. A loop of the jejunum was brought into the field and anastomosed to the gall-bladder—cholecystjejunostomy. The patient left the hospital four weeks later, May 15, 1913, with a gain in weight of twenty pounds. He remained well for eleven months, and about the middle of March, 1914, entered St. Benedictine Sanatorium at Kingston, New York, where he died April 13, 1914.

Carcinoma of the duodenum, with biliary obstruction; transfusion posterior gastro-enterostomy and cholecystogastrostomy; recovery.

CASE II.—S. A. (service of Dr. Erdmann), tailor, aged eighteen years. Entered the Post-Graduate Hospital, March 2, 1915, complaining of pain in the abdomen, loss of weight, and color. His illness began one year ago with the onset of pain in the epigastrium at irregular intervals, and only occasionally aggravated by food. For a considerable period of time relief from pain could be obtained by a movement of the bowels. Six months later the patient observed a mass in the upper portion of the abdomen which was somewhat movable, with the production of slight pain. Bowels have always been constipated. No history of blood in the vomitus or in the stools. Examination of the patient's abdomen suggested a tumor of the gall-bladder or pylorus. The pathological findings on roentgen-ray examination were (1) pylorus displaced upward and to the left; (2) residue in stomach to the left of median line; (3) residue in duodenum; (4) intestinal hypomotility. Roentgen-ray diagnosis: perforating ulcer of inferior and horizontal portion of duodenum, with distended gall-bladder. Urinary and Wassermann examinations negative. Stool examination on meat free diet: blood and absence of stercobilin. Ewald test meal, 50 c.c. obtained; free hydrochloric acid, 10; total acidity, 60. Blood examination: red blood cells, 3,712,000; hemoglobin, 40 per cent.; leukocytes, 7800; polymorphonuclears, 74 per cent.

Operation, March 23, 1915, revealed a large mass in the third and fourth portion of the duodenum. In addition there were two large retroperitoneal glands superimposed upon the tumor. The gall-bladder was found distended. Under the impression that the tumor might be an ulcerating process the peritoneum was incised over the involved portion of the duodenum and stripped back. One gland, the size of an English walnut, was removed, revealing a large hole in the transverse portion of the duodenum, with a slough of the intestinal mucosa plugging the opening. The finger introduced through the duodenal aperture encountered proximally, a complete obstruction. Inserting the finger a second obstruction was found, but not so complete as the one in the proximal segment. A cholecystogastrostomy and posterior gastro-enterostomy were done. The duodenal hiatus was repaired and the abdominal incision closed with drainage. Pathological reports of the specimen removed was that of adenocarcinoma.

Postoperative Course. The jaundice disappeared in five to six days and the patient was able to take regular diet at the end of seven days. On October 24, 1915, the patient was reëxamined and the tumor had become somewhat larger, but was giving him no clinical manifestations at this time. The patient had gained thirty pounds in weight, was eating regularly, and appeared in excellent physical condition.

Carcinoma of the common duct; cholecystogastrostomy; death.

Case III.—C. M. (service of Dr. Erdmann), painter, aged sixty-two years of age, entered the Post-Graduate Hospital on May 6, 1915, complaining of pain in the upper portion of the abdomen, slight pains in the umbilical region, which later became more severe and were located in the upper portion of the abdomen, but had no relation to food intake. Two weeks after onset of pain, noticed that he was jaundiced which steadily and persistently increased in intensity. At the same time noticed that his stools were large, bulky, and clay colored. Complains of headache, backache, and intense itching of the skin. Roentgen-ray examination of the gastro-intestinal tract after ingestion of bismuth meal showed overdistention of the bulbous duodeni with slight irregularity in the outline and with fixation of the duodenum. Blood examination: red blood cells, 4,200,000; hemoglobin, 70 per cent.; leukocytes, 10,300; polymorphonuclears, 74 per cent. Wassermann negative. Physical examination showed a markedly asthenic and emaciated patient with olive-green jaundice. Examination of the abdomen reveals a slight spasm of the upper muscles of the abdomen two fingers below the costal margin. Just below the free edge of the liver and near the median line is a round, palpable tumor, not particularly sensitive. The right kidney is independently palpable. Diagnosis: carcinoma of the gall-bladder and common duct.

Operation, May 14, 1915, revealed an extensive carcinoma of the terminal portion of the common bile duct, adenopathy along the superior border of the transverse colon. The gall-bladder was very much distended with bile and a cholecystogastrostomy was easily performed and the abdomen was closed with drainage.

Postoperative Course. The patient developed a dilated stomach twelve hours after operation. This yielded to repeated lavage. On the second day he had a moderate hemorrhage from his abdominal wound. He became progressively weaker and died of asthenic (pancreatic insufficiency) seven days after operation.

Carcinoma of the pancreas; hepaticoduodenostomy; death.

Case IV.—A. D. (service of Dr. Erdmann), lumberman, aged fifty-three years, entered the Post-Graduate Hospital on December 23, 1914; in a previous state of exhaustion. He complained of weakness and persistent jaundice. The history was of a gradual onset of jaundice, with slight pain in the right upper quadrant of the abdomen. The jaundice had increased steadily and persistently, with the development of rather marked pruritus. Patient on admission was in a rather profound cholemic state, with considerable mental haziness. Blood examination: red blood cells, 4,160,000; hemoglobin, 87 per cent.; leukocytes, 12,600; polymorphonuclears, 78 per cent.

Operation, December 24, 1914, revealed a carcinoma of the head of the pancreas involving the common duct. The gall-bladder was atrophic and contracted, while the hepatic duct was dilated to the diameter of 5 cm. A hepaticoduodenostomy was performed and the abdomen closed with drainage. The patient reacted slightly from his operation and gradually became duller and died at the end of seventy-two hours from progressive asthenia.

Carcinoma of pancreas; cholecystocolostomy; recovery.

Case V.—T. McC. (service of Dr. Erdmann), retired, aged seventy-one years, was seen in consultation by Dr. Erdmann with Dr. William Ewing and Dr. A. A. Smith in the fall of 1909. Patient complained of jaundice and gave a history of insidious but gradually increasing jaundice. Shortly after the development of the jaundice there was pain over the region of the gall-bladder and liver, due to the increasing distention of the gall-bladder.

Operation revealed a carcinoma of the pancreas with a greatly distended typical Couvoirsier gall-bladder and common duct, the latter being fully 5 cm. in diameter. A cholecystocolostomy was performed with a small Murphy button. Patient reacted from his operation. Button was passed on the eleventh day and there was general systematical relief from the itching, jaundice, and the cholemic condition. There was a marked improvement in the general bodily nutrition. Patient entirely recovered from the operation and was in a fair physical condition and died four and a half months after operation of an apoplectic stroke.

Carcinoma of pancreas and ampulla of Vater; posterior gastroenterostomy; cholecystostomy; recovery; secondary cholecystocolostomy; death.

Case VII.—L. C. (service of Dr. Erdmann), business man, aged fifty-eight years, gave a history of quiescent tuberculosis of the lungs with repeated exacerbations and at the time of examination gave evidence of a healed tuberculous lesion of considerable degree. His chief complaint was pain referred to the epigastrium, rather characteristic of a duodenal ulcer, and there was a tender appendicular zone. There was no pain in the back, stools were apparently normal, neither being large, copious, frequent, splashy, nor clay-colored. Blood examination revealed: red blood cells, 5,500,000; white blood cells, 12,000; hemoglobin, 82 per cent.; differential count: small lymphocytes, 18.5 per cent.; large lymphocytes, 7 per cent.; polymorphonuclears 72 per cent. Analysis of stomach contents, May 8, 1914, revealed a total acidity of 40; free hydrochloric acid, 4; combined, 16; no excess mucus, blood, or bile.

Examination of the feces on April 30, 1915, fifteen days postoperative, showed usual food remnants with large amount of free fat; decided excess of fatty acid; some carbohydrate fermentation; considerable unchanged starch and marked deficiency of bile; no blood revealed.

Operation on April 15, 1915, revealed an ulcer of the duodenum just beyond the pyloric ring with a mild stenosis of the pylorus due to an exudative infiltration. The appendix was found to be thickened. In addition to these findings a hard nodular mass about the size of an English walnut was palpated in the vulnerable portion of the pancreas. The operative diagnosis of this tumor was that of a carcinoma, but in the hope that it might prove to be inflammatory, a cholecystostomy was added to the posterior gastro-enterostomy and appendectomy.

Postoperative History. Gall-bladder drainage was continued for three and a half weeks; patient gained in weight. Toward the latter portion of his stay in the hospital and thereafter the stools were large and observed to contain free fat, were frequent in number, of splashy formation, and exceptionally offensive in odor. About June 1 patient noticed that he was becoming jaundiced and went to the country, and on June 16, three months after his original operation, he had a chill and a temperature of 103°. Upon physical examination a distinct tumor, fluctuant and tender, was found in the region of the gall-bladder, extending over to the midline. Patient was advised not to be operated upon until the gravity of the symptoms—distention, pain, jaundice—made operative intervention imperative. Palliative operation for biliary drainage was performed July 27; a very large gall-bladder, densely adherent to the liver and colon, was exposed. There was a hook-shaped prolongation of the gall-bladder upward and toward the median line, so that the fundus of the gall-bladder had apparently elongated 7 cm. in the three and a half months intervening since the first operation. The tumor of the pancreas had increased fully three times its original size and extended irregularly throughout the head and tail of the pancreas. On account of the exposed portion of the colon lying close at hand it was deemed advisable to perform the less satisfactory operation of cholecystocolostomy. This was readily accomplished, and in addition, drainage of the gall-bladder was instituted through a previous laceration in the gall-bladder near the liver surface. Patient reacted well and was progressing splendidly until the eighth day, when he began to ooze from his abdominal wound, and died on the eighth day from asthenia and hemorrhage.

Carcinoma of pancreas; hydrops of gall-bladder; cholecystostomy; choledochostomy; death.

Case VIII.—A. B. (service of Dr. Heyd), baker, aged sixty-one years of age, entered the Post-Graduate Hospital on June 22, 1915, complaining of sour eructations and jaundice. One month previous began to have sour stomach, which came on immediately after eating. A week later patient noticed that he was jaundiced, had a slight chill, and a temperature of 101.8°. Jaundice increased in intensity and stools became large, frequent, and clay-colored. Examination of the abdomen revealed a liver somewhat enlarged, extending 4 cm. below the right costal margin to the midclavicular line. A tumor mass about the size of an orange was palpated, suggesting a gall-bladder. Patient lost twenty-two pounds in weight since the onset of present trouble. Diagnosis: carcinoma of the pancreas.

Operation, June 28, 1915, revealed a gall-bladder moderately distended with mucoid material. Distention of the gall-bladder continued uniformly into a greatly dilated cystic duct. The latter passed down beneath the first portion of the duodenum before it joined the common duct. Exploration of the gall-bladder and common duct did not reveal any calculi. The head of the pancreas was hard, with rough, irregular outline. The cystic duct was incised and explored, the finger passed readily downward beneath the duodenum into the common duct and encountered an obstruction at the terminal portion of the common duct. A common-duct probe, however, passed readily beyond the mass into the duodenum. The hydrops of the gall-bladder evidently represented a pressure acholia as reported by Beaumont, Carno, Halstead, Kausch and others. A hydrops associated with malignancy of the pancreas is of peculiar importance from the operative stand-point as the findings of a gall-bladder filled with clear fluid is not proof of the occlusion of the cystic duct. Undoubtedly the hydrops in this case was due to an oversecretion by the mucous membrane of the gall-bladder and ducts, whereby the pressure in the common duct was raised so that the bile secretion was poured not into the hepatic ducts but into the hepatic capillaries and lymphatics. A cholecystostomy and a choledochostomy were performed. The patient was considerably shocked, but reacted fairly well. Eight hours after operation a slight oozing took place from the abdominal wound. This soon stopped and the patient did very well for twenty-four hours, when signs of peritonitis became evident and he died thirty-six hours after operation.

Conclusions. 1. All cases of obstructive jaundice are entitled to operative consideration. There is a certain definite percentage of cases that are cured because there has been a mistake in the diagnosis.

2. Any of the above operations are not prohibitive considering the severity of the disease and its hopeless outlook.

3. The immediate relief from itching, in addition to the prolongation of life, is an exceptionally strong argument for operation.

4. Operation obviates the development of "pressure pain" from increasing distention of the biliary apparatus.
5. These operations are advised solely as palliative procedures and as such their purpose must be clearly understood.

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THE WASSERMANN REACTION IN ITS RELATION TO TUBERCULOSIS.

By Captain Corydon G. Snow,

and

Captain Alexander T. Cooper,

MEDICAL CORPS, UNITED STATES ARMY.

(From the Laboratories of the United States Army General Hospital, Fort Bayard, New Mexico.)

This study was begun with the object of ascertaining the number of patients in this hospital who might give a positive Wassermann test in the presence or absence of syphilis, all patients being tuberculous unless otherwise noted.

It is recognized as a fact, by many physicians, that a positive Wassermann test may be obtained in tuberculous cases even in the absence of syphilis. Keyes, of New York,[1] states: "Some 5 to 10 per cent. of persons apparently free from syphilis give positive Wassermanns. The striking disagreement among published reports as to the influence of such conditions as tuberculosis, etc., is, perhaps, the best commentary on the uncertainty of the reaction as a sufficient criterion of the existence of syphilis." More interestingly, he states: "Only recently . . . I examined 40 inmates of a tuberculosis hospital in whom the Wassermann reaction had been reported positive. Thirty of these showed certain, or probable, clinical evidence of the disease. (Syphilis, it is presumed is intended.) Ten of them failed to show any such evidence. The blood of these ten was once again examined and . . . returned as positive. Another laboratory, employing two different antigens, obtained with cholesterinized antigen four positive and six negatives; with a lipoid antigen, one positive, one doubtful, and eight negatives. Under these circumstances I should be unwilling to go on the witness stand and swear that even the last survivor of all these tests has syphilis."

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[1] Some Clinical Features of the Wassermann Reaction, Jour. Am. Med. Assn., vol. lxiv, No. 10.

Thus, Keyes seems to conclude that tuberculosis must, to a certain extent, be excluded before a positive Wassermann test should be allowed to have any great bearing in the diagnosis of syphilis. Heimann,[2] of New York, also states that the sera of tuberculous individuals may give the reaction.

It was hoped that a suitable number of Wassermann tests on the sera of tuberculous patients in this hospital would throw some light on this question, *i. e.*, the value of a positive Wassermann in tuberculous individuals.

Technic. In all laboratory studies such as this it is essential for a clear understanding and conception that the technic employed should be fully described. Therefore, we will give, with as much detail as is possible within the limits of this paper, the technie followed in these experiments.

That there may be no doubt as to the various steps, we shall cover the entire ground, from the securing of the patient's blood to the end reading of the actual test.

All glassware used in our tests was chemically and bacteriologically clean. This we consider most important. Chemically pure NaCl to 0.9 per cent. in distilled water is used throughout in making the dilutions; and hereafter when salt solution is referred to this 0.9 per cent. solution is understood.

Securing the Patient's Serum. Place a constricting band around the arm about four inches above the elbow; when the veins at the bend of the elbow have dilated, paint the skin over those rendered prominent with tincture of iodin. Now plunge into the vein a large caliber sterile needle and collect the blood in a centrifuge tube. Allow this blood to remain at room temperature for about one-half hour, and then, with a sterile needle, gently separate the clot from the side of the tube. Care must be used not to break up the clot to any great extent, as, if this is done, some hemolysis will occur. After freeing the clot it is well to allow it to become more firm, by standing for another half hour at room temperature or, better, in the ice-box. The tubes are then centrifugalized at moderate speed for about ten minutes, when it will be found that a clear layer of serum is superimposed on the clot. Exactly 1 c.c. is now transferred to a small-sized test tube and inactivated in a water bath at 56° C. for one-half hour. Following the inactivation to the 1 c.c. of serum is added 4 c.c. of a 1.5 per cent. suspension of washed red blood cells in salt solution, the type of red blood cell depending on the hemolytic system used.

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[2] The Wassermann Reaction as a Clinical Test, etc., Jour. Am. Med. Assn., vol. lxiv, No. 18.

In these experiments sheep red cells were adopted, though any other might equally well be applied, owing to the fact that natural amboceptors are removed.

The serum, plus the red cell suspension, is now thoroughly mixed and placed in the incubator at 37° C. for one hour, and then either centrifuged and used immediately or allowed to stand in the ice-box over-night, when enough of the red cells will have settled to the bottom to allow of the removal of sufficient clear dilute serum for the test. This step dilutes the serum to 20 per cent., and at the same time, by the presence of red cells, removes by absorption any natural amboceptors that may be present. It is this dilute amboceptor-free serum that is used in the test.

Preparation and Titration of the Complement. Complement is furnished by the blood serum of healthy, full-grown guinea-pigs. Pooled serum will always have a higher titer than that from a single pig. As a routine we have used three pigs. They are etherized, and when fully anesthetized placed on their backs, and bled from the heart as follows: a 10 c.c. Luer syringe, with a large caliber needle, is used. It is important that the bevel of the needle point be somewhat short, the same as is used on lumbar puncture needles being very satisfactory, as otherwise the needle is very likely to perforate the heart, which will almost invariably result in the death of the animal from hemorrhage into the pericardium. Have also a dish of sterile salt solution to wash out the syringe between each bleeding, as otherwise the plunger will stick. When the pig is fully anesthetized, place the first finger of the left hand over the point of greatest cardiac pulsation, on the left side of the pig's chest, and the point of the needle opposite, on the right side. Thrust the needle through the chest wall, being careful to brace it so that it does not penetrate too deeply in the thoracic cavity at the first thrust. After the needle has penetrated the thoracic wall, direct it toward the point of greatest cardiac pulsation, as determined by the finger on the chest wall. In about one-half inch it will enter the ventricular cavity and blood will appear in the syringe. Gentle traction on the plunger will now enable one to secure 8 to 10 c.c. of blood. The needle is withdrawn and the anesthetic removed, firm pressure made over the heart for a second or two, and with the aid of artificial respiration, if necessary, the pig will soon recover and be no worse for the operation. Remove the needle from the syringe and expel the contents very gently into a centrifuge tube. Bleed in this manner three or four pigs, using a separate centrifuge tube for the blood of each. Allow these tubes to stand for a half hour, and free the clot in the same manner as in collecting patient's serum. Centrifuge and remove the clear serum, mixing that from the various pigs.

The complement should be secured on the morning used, and is to be titrated at once as follows:

Set up nine test tubes in a rack and dose each with 0.1 c.c. of pure complement. To each add salt solution, increasing in quantity from left to right as follows: c.c., 2.4, 2.6, 2.9, 3.2, 3.4, 3.9, 4.4, 4.9, 5.4, the resulting dilutions being 1 to 25, 27, 30, 33, 40, 45, 50 and 55 respectively. Mix the contents of each tube thoroughly. Now set up another series of tubes, ten in number, and dose each of the second series with 0.5 c.c. of diluted complement from the corresponding tube in the first series. The tenth tube of the second series receives no complement. Then to each of the ten tubes of the second series add the standard dose of dilute antigen, *i. e.*, 0.5 c.c., 1 c.c. of salt solution, and 1 c.c. of a 1.5 per cent. suspension of sensitized red blood cells (to be described later). When several antigens are used, including cholesterinized, the latter should always be used in the titration.

Ordinarily, hemolysis will occur in all tubes, but will not be absolutely complete in the higher dilutions after the half hour allowed for the complete reaction. The complement is used in the dilution indicated by the last tube to show complete hemolysis, generally 1 to 40. When antigen is used in this titration as above it is not necessary, in fact it is not well to use the complement stronger than its actual titer. When the titer is determined, dilute the pure complement as its titer indicates, and it is ready for use. Complement should never be used when it is over twenty-four hours old.

Preparation and Titration of the Antigen. In these experiments we used four different antigens, all alcoholic extracts: One, an alcoholic extract of guinea-pig heart, made by grinding the heart muscle that has previously been thoroughly washed in salt solution and freed from fibrous tissue and fat, with powdered glass, and adding absolute ethyl alcohol in the proportion of 1 gram of heart muscle to 25 c.c. of absolute alcohol; this mixture is then incubated at 37° C. for forty-eight hours and then kept at room temperature for the same period, being shaken at frequent intervals; filter and titrate as below described; this was called Antigen No. 1. Antigen No. 2 was the same as Antigen No. 1 plus cholesterin added to 0.4 per cent. Antigen No. 3 was made in the same way as No. 1, except that human heart muscle from a known syphilitic was used in the proportion of 1 gram of heart muscle to 10 c.c. absolute alcohol. Antigen No. 4 was the same as No. 3, with cholesterin added to 0.4 per cent. These antigens were titrated as follows:

A series of seven tubes is set up in a rack and dosed as shown in Table I.

TABLE I.

Pure antigen. c. c.	Plus 0.9 per cent. NaCl, c.c.	Dilution.
1.0	1.0	1 to 2
1.0	3.0	1 to 4
0.5	2.5	1 to 6
0.5	3.5	1 to 8
0.5	4.5	1 to 10
0.5	5.5	1 to 12
0.5	6.5	1 to 14

Two series of seven tubes each are now set up, the first, or series "A," is dosed with 0.5 c.c. of a known negative serum, prepared and diluted as above described; the second, or series "B," receives 0.5 c.c. of a dilute double plus positive serum. These sera must be treated in the same manner as described under the directions for collecting patient's serum. The first tube of each series now receives 0.5 c.c. of a 1 to 2 antigen, the second, 0.5 c.c. of a 1 to 4, and so on. Now add to all tubes, 0.5 c.c. of titrated and diluted complement and 0.5 c.c. of salt solution. Incubate one-half hour at 37° C. in a water bath and add 1 c.c. of a 1.5 per cent. suspension of sensitized red blood cells. Return to water bath and read results in one-half hour. If both antigen and serum are acting right, series "B" should show no hemolysis, and series "A" complete hemolysis in all save the first and perhaps the second tubes. The last tube in series "A" that fails to completely hemolyze is the index of the anticomplementary strength of the antigen. A good antigen should always bind the complement in a dilution of 1 to 10 to 1 to 14 in the presence of a double plus serum. The dilution at which the antigen is to be used is at least four points removed from the anticomplementary point. No antigen is used in which the anticomplementary point is higher than 1 to 4. When possible we always use more sera in titrating antigen than the two above noted, *i. e.*, a single plus and a plus minus as well as the negative and double plus sera. The antigen for use is diluted with salt solution according to its titer. The titration of Antigen No. 1, or alcoholic extract of guinea-pig heart, showed it to be anticomplementary at a dilution of 1 to 2 or lower. It would bind complement with double plus syphilitic serum at 1 to 12. It was used at 1 to 6. Antigen No. 2, or cholesterinized alcoholic extract of guinea-pig heart, was anticomplementary at a dilution of 1 to 2 or lower. It would bind complement with double plus syphilitic serum at 1 to 24; it was used at 1 to 6. Antigen No. 3, or alcoholic extract of human heart, was anticomplementary at a dilution of 1 to 2 or lower. It would bind complement with double plus syphilitic serum at 1 to 14. It was used at a dilution of 1 to 9. Antigen No. 4, or cholesterinized alcoholic extract of human heart, was partially anticomplementary at a dilution of 1 to 6 or lower. It would bind complement with double plus syphilitic serum at 1 to 24. It was used at 1 to 14.

The Amboceptor. Prepare washed sheep red blood cells as below described and proceed as follows: Select a full-grown, healthy rabbit and shave an area of the abdomen about one inch square fairly low down and to one side of the median line. Draw up, in a sterile Luer syringe, 4 c.c. of pure washed sheep red blood cells. Sterilize the shaved area of the rabbit with tincture of iodin and, lifting the skin away from the viscera, thrust the needle through, making sure that it has completely penetrated the abdominal wall, as otherwise an abscess may result. Inject the red blood cells, withdraw the needle, and seal the wound thus made with collodion. This injection is repeated at weekly intervals, increasing the dose 1 c.c. each week until 8 c.c. of red blood cells have been given in one dose. The 8 c.c. dose is repeated and twelve days later the animal is bled from the marginal ear vein, removing about 30 c.c. of blood, which is allowed to clot; it is then centrifugalized and placed in sterile containers.

Two courses may now be followed: If a refrigerating plant is at hand the pure serum may be kept frozen in its original containers, or it may be diluted to 1 to 100 in salt solution and pure phenol added to 0.5 per cent. Experiments show that this dilution with phenol does not injure the amboceptor or interfere with the test.

It is our custom to titrate the amboceptor before making the dilution and at frequent intervals thereafter. To titrate the pure amboceptor proceed as follows: Make an initial dilution of 1 to 200 in salt solution. Set up a series of ten tubes: Series "A." Add to each, 0.1 c.c. of dilute amboceptor. Now to each tube add a 1.5 per cent. suspension of washed sheep red blood cells, the quantities increasing from left to right as follows: C.c., 0.9, 1.4, 1.9, 2.4, 2.9, 3.4, 3.9, 4.4, 4.9, 5.4, thus making dilutions of from 1 to 10 to 1 to 50 of the dilute 1 to 200 amboceptor, and of 1 to 2000 to 1 to 11,000 of the pure.

Now set up a second series of ten tubes, Series "B." Transfer to each tube 1 c.c. of the amboceptor red blood mixture from its respective serial tube and incubate one hour at 37° C. Place the tubes in a centrifuge for fifteen minutes at moderate speed. For Series "B," small test tubes or centrifuge tubes are most convenient, so that unnecessary handling of the solution may be avoided. Pour or pipette off the clear supernatant fluid and add

2.5 c.c. of salt solution and 0.5 c.c. of dilute and titrated complement. Mix well and incubate at 37° C. in a water bath for one hour and read results. The most dilute tube to show complete hemolysis is the index of the strength of the amboceptor, and is the strength at which it should be used. It will be noticed that in all these titrations conditions are rendered as nearly similar as possible to those under which the various reagents will have to act in the actual test. The titer of the amboceptor now having been determined, it is either frozen or preserved by dilute phenol and kept ready for use. We do not use free amboceptor, but from it make sensitized red cells. A 1.5 per cent. suspension of red cells is made in 0.9 per cent. NaCl, and to this is added enough pure or dilute phenolized amboceptor to make the total volume desired equal the amboceptor dilution required by the titer. The arbitrary dose of sensitized red blood cell suspension used in the test being 1 c.c., the titration, as seen above, is made accordingly. This red cell and amboceptor suspension is now incubated for one hour at 37° C., removed and centrifuged. Large centrifuge tubes are here almost a necessity. The supernatant fluid is poured off and the original volume made up with salt solution. Red blood cells will absorb only their maximum dose of amboceptor, consequently by this step we avoid a surplus of amboceptor, and at the same time insure a sufficient quantity.

Again, a red blood cell that is saturated or sensitized with amboceptor is more quickly responsive to complement than one which must absorb both at the same time. Practically, it is our custom to place a larger amount of amboceptor in the red blood cell suspension than is actually required by the titer, for, as above noted, the red blood cells can only absorb their maximum dose, the surplus of amboceptor being discarded when the supernatant fluid is poured off after centrifugalizing. This mixture, after the red cells have absorbed their dose of amboceptor and the surplus discarded, the original volume being made up with salt solution, is called sensitized red blood cells.

Preparation of Washed Red Blood Cells. Any hemolytic system may be used in this technic, it only being necessary that amboceptor and red blood cells correspond. As above noted, we have used sheep red blood cells, and by the saturation step have eliminated natural amboceptors.

Full-grown healthy sheep are selected, placed on a suitable table, and bled either from the jugular or one of the leg veins. In either case constriction is made on the proximal side of the vein, causing it to dilate. The overlying skin is then shaved and rendered sterile with iodin. The same type of syringe and needle that is used in securing complement is employed and the blood transferred immediately to a flask containing about 75 c.c. of a 1.5 per cent. solution of sodium citrate in salt solution. To prevent clotting of the blood in the syringe, about 2 c.c. of this solution should be in the barrel of the syringe before withdrawing the blood. This blood-citrate mixture is thoroughly shaken, placed in large centrifuge tubes, and centrifugalized for five to ten minutes. The citrate is then poured or pipetted off and replaced by salt solution. This new suspension is now thoroughly shaken and again centrifugalized. This washing process must be thoroughly done and repeated at least four times. The thick mass of red blood cells left from the last washing are the pure washed red cells referred to in the foregoing paragraphs.

Application of the Reagents to the Test. Five tubes are used, four containing antigen and one control. The contents of these tubes may most clearly be shown in Table II:

TABLE II.

	Tubes Nos.				
Contents.	1.	2.	3.	4.	
20 per cent. dil. patient's serum	0.5	0.5	0.5	0.5	0.5
Antigen, No. 1, G. P. H.	0.5	0	0	0	0
Antigen, No. 3, H. H.	0	0.5	0	0	0
Antigen, No. 4, C. H. H.	0	0	0.5	0	0
Antigen, No. 2, C. G. P. H.	0	0	0	0.5	0
Complement	0.5	0.5	0.5	0.5	0.5
NaCl, 0.9 per cent.	0.5	0.5	0.5	0.5	1.0

Mix the contents thoroughly and incubate in a water bath at 37° c. for one half hour, and add to each tube, 1 c.c. of sensitized red blood cell suspension. Return to water bath and hold at same temperature for one hour, then remove, place in the ice-box overnight, and the following morning read the results. Following the addition of sensitized cells the tubes must be again thoroughly shaken, and it is best to repeat this shaking frequently throughout the second incubation.

Readings were made on a + + complete binding scale, the symbols used in reporting the findings being: —, ±, +, and + +. The symbols used in recording our reactions differed from the above in that they were more detailed: —, ∓, ±, +, and + +. Only those sera which gave complete complement binding or a + + reaction with all antigens were reported as + + positive.

To explain these symbols: + + signifies complete binding of the complement with no trace of hemolysis after remaining overnight in the ice-box. + signifies the reaction in which there is almost complete binding of the complement but with a trace of hemolysis. ± signifies the reaction in which there is about 50 per cent. or slightly less of the red blood cells hemolyzed. ∓ the reaction in which there is almost complete hemolysis, but where there still remains in the bottom of the tube a slight residue of cells. — is the reaction in which complete hemolysis has occurred.

To place these readings on a clinically satisfactory basis, they were interpreted on the scale above noted, *i. e.*, —, ±, +, and + +.

The following table illustrates the method used:

TABLE III.

Tube No. 1. Ant. No. 1.	Tube No. 2. Ant. No. 3.	Tube No. 3. Ant. No. 4.	Tube No. 4. Ant. No. 2.	Reading.
−	−	−	−	Negative
∓	∓	∓	∓	Negative
−	−	∓	∓	Negative
∓	∓	± or +	± or +	±
∓	∓	++	++	±
−	−	++ or +	++ or +	±
± or +	± or +	++	++	+
++	++	++	++	++

It may be well to state that the above technic is a slightly modified form of that devised by one of us after considerable experimentation, and applied in about 4000 tests, with extremely satisfactory results, both from a treatment control basis and for diagnostic purposes.

Discussion. That the Wassermann test has proved syphilis a much more protean and undiagnosed disease than was formerly supposed by medical men is now ancient history. Landouzy,[3] of France, has for twenty years been preaching the extraordinary, the unbelievable frequency of syphilis. Wile and Stokes,[4] speaking of early syphilis, state: "For the most part tabetics and paretics have had so-called mild early syphilis; indeed, in many cases so inconspicuous that the patients remained in total ignorance of the infection." Veeder and Jeans[5] state: "A positive Wassermann reaction may be the only symptom of syphilis for many months or years." Habermann[6] states: "Careful, in fact the most careful, history taking is necessary with all our alertness and sharpness set into activity, and with the aid of the Wassermann test we shall discover a very large number of congenitally syphilitic whom we never suspected before."

If syphilis is then, as many authorities contend, a widespread and frequently unrecognized infection, and as we know tuberculosis is a much more widespread disease, there must be a considerable overlapping of these infections, so that the physician must consider and treat many patients who have latent, incipient, active, or inactive tuberculosis, and at the same time syphilis in its varied forms. And if, as many physicians believe, tuberculosis must, to a certain extent, be eliminated before a positive Wassermann reaction is of great value in determining the presence of latent or obscure syphilis, then, manifestly, the Wassermann reaction is of little value as an aid in detecting the presence of syphilis in tuberculous cases. Such a conclusion we were not ready to accept on the evidence offered.

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[3] Presse Médicale, Paris, May 13, 1915, No. 21, pp. 161–168.

[4] Jour. Am. Med. Assn., vol. lxiv, No. 18.

[5] Diagnosis and Treatment of Late Hereditary Syphilis, Am. Jour. Dis. Child., October, 1914, p. 283.

[6] Hereditary Syphilis, Jour. Am. Med. Assn., vol. lxiv, No. 14.

In the following *résumé* of our experiments the reaction reported is the clinically interpreted result of our laboratory findings, and does not, unless so stated, have special reference to the readings of individual tubes. The number of tuberculous patients examined was 290. The number of Wassermann tests on these patients, 1862. All patients giving a + or + + reaction with the noncholesterinized or Nos. 1 and 3 antigens gave a + + reaction with cholesterinized or Nos. 2 and 4 antigens.

The number of patients presenting a double plus (+ +) reaction was 27. Of these 27 the number having a clear history of syphilis or syphilis admitted or diagnosed was 16. Remaining, 11. Of these 11, those who admit having initial penile sores were 5, as follows:

1. (L. S.) Sore on penis in 1910, appearing one week to ten days after intercourse. A large scar still remains. Has moderate general lymphatic enlargement. Diagnosed, January, 1913, as inactive pulmonary tuberculosis. Sputum has never been found positive for tubercle bacilli. Has had a repeated + + Wassermann reaction.

2. (E. G.) Sore on penis in 1903, one week to ten days after intercourse. This healed in three weeks. He was circumcised while he had this sore, and he states the sore did not spread around the incision. At the present time he has quite marked general lymphatic enlargement. Wassermann reaction repeatedly + +.

3. (A. J.) Penile sore in 1910. Transferred to this hospital with the diagnosis "tuberculous abscesses of right axilla, and marked enlargement of substernal glands." On his history chart various doctors have repeatedly written "no physical sings of pulmonary tuberculosis" or "inactive lesion." Wassermann reaction + +.

4. (A. R. Mc.) Had a small penile sore after exposure in 1908. At the present time he has tachycardia and cardiac arrhythmia. Marked pleuritic adhesions to pericardium, as shown by the roentgen ray. Moderate general lymphatic enlargement. Wassermann reaction + +. Has active pulmonary tuberculosis.

5. (N. P.) Penile sore and bubo in 1902, following exposure. At the present time he has quite marked general lymphatic enlargement. Active pulmonary tuberculosis. Wassermann reaction, + +. Of these 5 patients we have no hesitancy in making a diagnosis of syphilis in all of them. Of the 11 cases, those who deny initial lesions but give a + + Wassermann test and who present a history or symptoms referable to what we consider syphilis there are 4.

6. (J. A. M.) Aged thirty-six years. Thinks he had what he would call "venereal warts" in 1901. In January, 1915, a diagnosis of Raynaud's disease was made. His history states a blister formed

on the top of the third toe, left. This left an ulcer which slowly healed. Wassermann reaction + + both in the army hospitals at Manila and San Francisco. Has received one intravenous injection of salvarsan because of his + + test. At present has no symptoms of Raynaud's disease. Wassermann reaction here repeatedly + +. In this hospital about six months, and has recently been returned to duty.

7. (L. Z.) Denies all venereal diseases. We subsequently discovered that he had a record of gonorrhea in 1913. His father died of stomach trouble (?), aged fifty-six years. Mother died of stomach trouble (?), aged fifty-four years. This patient was diagnosed pseudoleukemia in 1902, in Germany, because of enlarged lymph glands (patient's statement). He has had stomach trouble the past year and has been jaundiced at irregular intervals. Has very marked general lymphatic enlargement. His history states that he had persistent soreness of throat in 1910. Persistent headache and dizzy spells in 1911. Wassermann reaction + +; has active pulmonary tuberculosis.

8. (E. P. M.) Denies all venereal diseases. Has had markedly enlarged lymph glands of the neck since 1905 when in the Philippine Islands. These glands have been operated on seven times. While in the Philippine Islands he states he took mercury by mouth for one month. This he believes slightly reduced the size of the glands. He had "ugly sores with pus in" over the body in 1908–9. Has chronic arthritis in right knee joint, and chronic laryngitis, also marked general lymphatic enlargement. Lymphadenitis of neck and axilla. Wassermann reaction, + +. Has active pulmonary tuberculosis.

9. (G. A. B.) Denies all venereal diseases. Father died of "brain trouble, 'stroke,'" aged fifty-four years. For the past two years has had atrophy of right trapezius muscle and posterior fibers of right deltoid, cause of atrophy undetermined. In May, 1914, he stopped working in the laundry for two weeks because of laryngitis. Has moderate general lymphatic enlargement. Wassermann reaction repeatedly + +; has inactive pulmonary tuberculosis.

In these cases (6 to 9 inclusive) we believe a diagnosis of syphilis in some form or other justified; the diagnosis being based on either history, symptoms, or physical signs, or the combination of these. This leaves the cases giving a + + Wassermann reaction, in whom the diagnosis of syphilis may be classed as doubtful, in number 2.

10. (W. M. W.) This man has no discoverable history or physical signs of syphilis. Because his Wassermann reaction was + +, he asked for and has received several intravenous injections of salvarsan. This has had no effect except that he thinks it possibly has improved his cough. Has had active pulmonary tuberculosis,

but his general condition is such that he will probably be returned to duty very soon. Wassermann reaction + +. This patient also shows a single + Luetin reaction.

11. (E. P. M.) Denies all venereal diseases. No physical signs of syphilis at present except moderate general lymphatic enlargement. There is noted on his history chart, by the several physicians who have had him in charge since 1909, "No present evidence of tuberculosis;" "no positive evidence of tuberculosis at present;" "possibly slight inactive lesion at right apex;" temperature unaccounted for;" "no signs of activity;" "inactive lesion." At present he has active pulmonary tuberculosis, however. Wassermann reaction repeatedly + +. This patient has received two intravenous doses of salvarsan, and his ward surgeon reports that physical signs that might be referable to tuberculosis indicate marked improvement.

In these last two cases (10 and 11) there is possibly as much evidence for syphilis as against. They are both soldiers and may be concealing the real facts for fear of getting a diagnosis with a "not in line of duty" status.

There are then but 2 out of 290 tuberculous patients who have a + + Wassermann in whom we can find no history or symptoms of syphilis at present, or less than 0.7 per cent. Surely it is a negligible percentage. This 0.7 per cent. may or may not have syphilis. It is well to remember at this point that the reactions as we report them in this series of cases have reference to the clinical interpretation of our tests unless specially stated to the contrary, and that the 27 cases above considered gave complete complement-fixation with all antigens.

Nineteen of the 290 tuberculous patients had a Wassermann reaction which we read as +. Of these 19 we found 8 who presented a clear history of syphilis or had been diagnosed syphilis on sick report. Seven of the remaining 11 either have a history of penile sores or have had or have at present more or less symptoms and physical signs which we consider referable to a latent syphilitic infection. These 11 patients are as follows:

1. (C. E.) Sore on penis in 1912. This patient states that he was under treatment at Hot Springs, Arkansas, for skin trouble and rheumatism. He states that his Wassermann test at that place was + +. Wassermann test at this hospital was +.

2. (J. B. C.) Sore on penis ten years ago; no other history referable to syphilis. At present he is under observation here for pulmonary tuberculosis. Wassermann reaction at this hospital, ± and +.

3. (A. J. H.) This patient states that he had a sore on his penis ten years ago which he thinks was diagnosed chancre. He has a large amyloid liver and spleen, first detected one year ago. Wassermann reaction, +. This patient, within the past few days, has

died. Autopsy showed decidedly suspicious evidence of a syphilitic infection.

4. (D. P. K.) Small penile sore in 1911. This sore appeared one week to ten days after exposure. He was in the hospital ten days because of it. At the present time he has a marked penile scar and moderate general lymphatic enlargement. Wassermann reaction, +.

5. (M. G. C.) Penile sore nine years ago. Markedly enlarged glands of the neck at the present time; chronic laryngitis; moderate general lymphatic enlargement. Wassermann reaction, ± and +.

6. (V. W.) Sore on penis in 1900. His history states that he had marked general lymphatic enlargement in 1912. Moderate at present, however. Wassermann reaction, +.

Of these 6 we are of the opinion that at least 5 have latent syphilis. This opinion is based on their past history and present physical signs. Case No. 2 may or may not have latent syphilis. There remain 5 patients whom we read as +. These patients' sera gave a ± with the lipoidal antigens, but a strong + + in the cholesterin tubes. When this occurs the reaction is reported as +.

7. (J. H. D.) Denies initial lesion. Has had chronic laryngitis since 1903. His history states "slight nodule, globus major, both testicles, January, 1903." "Epilepsy, September, 1912." Wassermann reaction, +.

8. J. F. D.) Initial lesion denied. Has had marked chronic rhinitis since 1907. Has a marked tremor of hands; uses alcohol to excess. Wassermann reaction, +.

9. (H. K.) Aged twenty-five years. Denies venereal diseases. Has had persistent frontal headache for past year. Had symptoms suggestive of iritis one year ago. Eyes were painful and light hurt them. He has slight general lymphatic enlargement. For the past two or three years, he states, he has worked most of the time in the venereal wards of the military hospitals, taking care of syphilitics. He had frequently sores on lips and fingers. Wassermann reaction, +.

10. (J. E. T.) Nothing definite in this patient's history or physical examination referable to syphilis. Wassermann reaction, +.

11. (J. F. D.) Father died of heart trouble (?), aged forty years. Mother died of an unknown cause when a young woman. Sister died of heart trouble, aged twenty years. Venereal infection denied. Wassermann reaction, +.

Of these last cases from 7 to 11 we consider that the history, etc., justifies a diagnosis of syphilis in at least two cases, 7 and 9. The others, 8, 10 and 11, may or may not have latent syphilis. This gives, of the 19 cases analyzed presenting a + reaction, 15 in whom we consider a diagnosis of syphilis in some form justified.

Four tuberculous patients, then, in 290, or 1.3 per cent., give a + reaction, and may or may not have syphilis. These 4 giving a + reaction with the two who have a + + reaction who are questionably syphilitic, make slightly over 2 per cent. of 290 tuberculous patients whose sera were tested which give a + to a + + reaction who were doubtfully syphilitic. For all practical purposes surely this too is a negligible percentage.

Of the 244 patients remaining, 26 have a consistent and repeated + + reaction with both cholesterinized antigens, and a clear-cut negative reaction with the non-cholesterinized antigens. Of these 26, 3 admit syphilis, have been so diagnosed and have received treatment for the same. Three others are probably syphilitic. This opinion is based on their present physical signs and past history. Ten are possibly syphilitic, but not probably so, having a history of possible suspicious symptoms and a few more or less suspicious physical signs which might point to an obscure, or latent, infection of syphilis. The remaining 10 cases are frankly negative, both in their past history and present physical signs, yet the sera of these 10 cases completely bound the complement with cholesterinized antigens.

It is interesting to note here, however, that a non-tuberculous hospital corps soldier (E. M. McC.) who denied an initial lesion, having no physical signs of syphilis but giving a + + reaction with the cholesterinized antigens, though negative with the non-cholesterinized, had a + + reaction with the non-cholesterinized antigens after receiving one intravenous injection of salvarsan. Also, that one tuberculous patient (W. R. C.) with negative physical signs and a negative history of syphilitic infection, showing a + + reaction with the cholesterinized antigens, but negative with the non-cholesterinized, had a + reaction with the non-cholesterinized antigens twenty-four hours after an intravenous injection of salvarsan, and the following day, or forty-eight hours after receiving this injection, gave a + + reaction with the cholesterinized but negative with non-cholesterinized antigens. (This patient's serum has since returned to a clinically interpreted + reaction.) This patient has recently stated that a chronic persistent eczematous condition on his chest, having an area of three or four inches in diameter, which was of many years' standing, has, after the salvarsan, entirely healed. This may have no bearing on the case as regards syphilis, owing to the well-known beneficial effect of arsenic on chronic skin diseases.

Of the 218 remaining cases, 47 were negative with non-cholesterinized, and + with both cholesterinized antigens or + with cholesterinized human heart antigen and + + with cholesterinized guinea-pig heart antigen. Of these 47, 5 are probably syphilitics, having a history of small, quickly healing, penile sores, followed by more or less obscure symptoms and physical signs which might be interpreted as latent syphilis. Of the 47 cases, 15 others might possibly be classed as syphilities, though not probably so. Seven of these 15 patients give a history of superficial penile "abrasions (?)" following intercourse, which healed quickly. The remaining 8 patients of this 15 possibly give obscure physical signs referable to a latent syphilitic infection, but deny an initial sore of any kind. Twenty-seven, the remainder of the 47, do not admit infection, neither have they, in our opinion, any physical signs or symptoms of a syphilitic infection.

Of the 171 remaining cases, 34 were negative with the non-cholesterinized antigens, and gave a ± with both cholesterinized antigens or a + with the cholesterinized guinea-pig heart antigen and a + with the cholesterinized human heart antigen. One patient of these, 34 (H. T.), gives a frank history and admission of chancre which persisted for six weeks to two months, healing promptly on an intravenous injection of salvarsan. Six of these cases may be classed as possibly syphilitic but not probably so. Two of these patients have a history of penile sores (chancroids?). They, with the four others, have vague and indefinite physical signs which might possibly mean latent syphilis, but not probably so. Twenty-seven of this series of 34 present no physical signs or symptoms of syphilis, and have an entirely negative history.

The remaining 137 patients have a negative reaction throughout with all antigens. It might be well to state here that in our experience, as well as in that of most every army surgeon, the so-called typical initial lesion of syphilis is only present in about 25 to 50 per cent. of cases which afterward become frankly syphilitic.

A possible explanation of the positive complement fixation reactions in tuberculous patients when using cholesterinized antigens is, that inasmuch as cholesterin probably originates as a proteid cleavage product from destroyed tissue cells, it is reasonable to suppose that in such conditions as tuberculosis where marked cell destruction and necrosis is present, pathological amounts of cholesterin will be found, and that the body will react to it as to any antigen by the production of antibodies, and that these antibodies will, when the Wassermann test is applied and a cholesterinized antigen is used, cause binding of the complement. This, if true, might possibly account for the high percentage of positive reactions in non-syphilitic tuberculous patients.

At least 90 per cent. of those patients who have conjoined syphilis and tuberculosis contracted syphilis one to several years prior to the diagnosis of tuberculosis. Some evidently have congenital syphilis. Twenty-two of the 44 patients whom we consider syphilitic have received antisyphilitic treatment at irregular intervals, possibly more or less adequate. Whether the majority of these patients who are syphilitic as well as tuberculous would be benefited to any extent, as far as their symptoms referable to tuberculosis are concerned, remains an open question; certainly a few have been so benefited. At least the probability that in the development of tuberculosis one of the contributing factors may have been a prior existing syphilitic infection in 10 to 20 per cent. of tuberculous cases certainly is a condition that may well challenge our attention.

SUMMARY.—The summary of our work is as follows:

1. Number of tuberculous patients tested	290
2. Number of + + reactions (*i. e.*, complete fixation of complement with all antigens)	27
Of the 27, those who have a clear history of syphilis, or admit infection and treatment, or who have been diagnosed syphilis on sick report heretofore, number	16
Number not previously diagnosed before admission to this hospital	11
Of these 11, those who admit penile sores following exposure, and now present what we consider definite physical signs of syphilis, number	5
Of the 11, those who deny any initial lesion, but have most suspicious physical signs and history that we believe syphilitic, number	4
Doubtful or negative syphilitics giving complete complement fixation with all antigens (*i. e.*, with non-cholesterinized as well as cholesterinized) are	2
3. Number of patients giving a + reaction (*i. e.*, 50 per cent. to almost complete fixation of complement with the non-cholesterinized antigens, and complete fixation with the cholesterinized antigens, is	19
Of these 19, those who have a clear history of syphilis or have been diagnosed syphilis on sick report, number	8
Of these 19, those undiagnosed before admission to this hospital, but who give a history of a suspicious primary sore and a history of suspicious symptoms following, and having physical signs which we believe referable to latent syphilis, number	5
Of the 19, those who deny an initial lesion, but have physical signs and symptoms such that we believe a diagnosis of syphilis is justifiable, number	2
Of the 19, those who may be classed as negative or doubtfully syphilitic, number	4
Total + and + + reactions	46
Per cent. reactions in 290 patients	15.6
Number of the 46 who may be classed as doubtfully syphilitic (Percentage, 2 per cent. plus.)	6
4. Of the remaining 244 patients, those having complete complement binding with the cholesterinized antigens, negative with the non-cholesterinized antigens, number	26
Of these 26, those who have been diagnosed syphilis, presenting a more or less typical history, etc., number	3
Of the above 26, those whom we consider probably syphilitic, number	3
Of these 26, those whom we consider possibly syphilitic, not probably so, number	10
Remainder of the above 26 whom we consider frankly negative, both in history, symptoms and physical signs, number	10
5. Number of the remaining 218 tuberculous patients having almost complete complement binding with both cholesterinized antigens, or almost complete with the cholesterinized human heart antigen and complete with the cholesterinized guinea-pig heart antigen; no binding with non-cholesterinized antigens, is	47
Of these 47, those whom we consider probably syphilitic number	5
Number of these 47 whom we consider might possibly be classed as latent syphilitics, not probably so however, is	15
The remainder of the 47 whom we consider frankly negative as to syphilis in history, symptoms, and physical signs, amounts to	27
Per cent. of 201 tuberculous patients frankly negative as to syphilis, whose sera almost completely binds, or completely binds, complement with cholesterinized antigens; no binding with non-cholesterinized antigens, is	19+

6. Number of the remaining 171 tuberculous patients whose sera binds complement, 50 per cent. with cholesterinized antigens, or 50 per cent. cholesterinized human heart antigens and almost completely binds complement with cholesterinized guinea-pig heart antigen; no binding with non-cholesterinized antigens, is 34
   One of the patients admitting syphilis and treatment 1
   Of the remaining 33, those whom we consider possibly syphilitic, not probably so, number 6
   The remainder of the 34 patients we consider frankly negative syphilitics in history, physical signs, and symptoms; in number is 27
   Per cent. of 201 tuberculous, frankly non-syphilitic patients whose sera is negative with non-cholesterinized antigens, but partially to completely fixed complement with cholesterinized antigens . . . 31 +
   (This percentage excludes all the syphilitics—known, probable, and possible—of the 290 patients.)
7. Total number of the 290 tuberculous patients who are certainly syphilitics, is 44
   Per cent. syphilitic, 14.8.
   Total number of the 290 tuberculous patients who are syphilitic and probably syphilitic is 58
   (This includes the six doubtful, whose sera gave a double plus or a plus reaction.)
   Per cent. syphilitics or probably syphilitics, 20.

Conclusions. As a result of these experiments, we are firmly convinced that tuberculosis need not, in the absence of syphilis, present a positive Wassermann reaction. That it does so under certain circumstances is equally evident, as seen both from the literature and the above-noted facts. Wherein then lies the reason for these contradictory statements?

It is our opinion that the answer is simple, and is to be found in the use of cholesterin in the antigens employed, and possibly in other technical errors originating in the desire to simplify the test at the expense of accuracy. Careful titrations, accurate dosage, and unlimited trouble are necessary, particularly as we have to deal with elements of whose exact nature we remain in ignorance.

When speaking of antigens, we offered a purely tentative suggestion as to the reason cholesterin might be, in itself, responsible for false positive reactions in tuberculous patients who were clinically free from syphilis. It must be remembered that this is a suggestion only, and is not based on any known facts or experimental data.

Regarding the clinical histories as given in this article, we have not attempted to go into detail but have merely given a few of the most suggestive facts bearing on syphilis. However, these patients were carefully and completely examined by us at the time of their tests, and all patients, including those we mention, classed as non-syphilitic as well as syphilitic are equally carefully examined at frequent intervals by their ward surgeons.

Finally, tabulating our results, we conclude: 1. That the percentage of non-syphilitic, tuberculous patients whose blood may bind complement with non-cholesterinized antigens is so small as to be practically negligible. Complete complement-fixation *i. e.*, a strong + + Wassermann reaction with non-cholesterinized antigen, in a tuberculous patient, is as adequate presumptive evidence of syphilis as it is in a non-tuberculous.

2. That the sera of non-syphilitic tuberculous patients may give partial ± to complete + + complement-fixation with cholesterinized antigen in about 31 per cent. of cases.

We desire to express our thanks to Colonel Bushnell and other members of the Army Medical Corps on duty at Fort Bayard, New Mexico, for the aid and encouragement extended to us during this work.

SUBACUTE YELLOW ATROPHY OF THE LIVER.

By Alexander Fraser, M.D.,

INSTRUCTOR IN PATHOLOGY IN THE UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE; ASSISTANT PATHOLOGIST TO ST. VINCENT'S HOSPITAL.

(From the Laboratories of Pathology at the University and Bellevue Hospital Medical College, New York City.)

A lesion of the liver has been described in which the essential pathological changes are represented by extensive hemorrhage and necrosis followed by regeneration of liver tissue and fibrous replacement. The clinical picture varies, the majority of cases being of short duration (averaging fourteen days), and the chief features jaundice and severe toxemia, while at the other extreme the course may extend over a period of months or even years and the symptoms present the typical picture of portal obstruction as seen in Laennec's cirrhosis. Though the clinical picture varies, the anatomical changes in the liver are essentially the same, the only correlation between the two being that in the more rapidly fatal cases necrosis predominates, while in the more protracted cases regenerative and fibrotic changes are more evident. The more acute cases have been included under the name of "acute yellow" or "acute red atrophy of the liver," and the more protracted cases under the name of "subacute atrophy of the liver," though undoubtedly cases have been described through a mistaken notion of their pathogenesis, under various other names, such as "multiple nodular hyperplasia," "multiple hemangioma disseminata,[1]" "atrophic cirrhosis," etc. The published cases represent all ages up to fifty-three. The more protracted cases and especially those showing symptoms of portal obstruction—at least those definitely recognized as such—are extremely rare, and the statistics would seem to indicate that they are more common in children—4 out of the 5 cases reported by McDonald and Milne[2] having occurred in children of seven years of age or under. It is partly on account of the rarity of definitely recognized cases of this type that I think it worth while to publish the following, which occurred in a boy aged six years, extended over a period of seven months and presented the clinical picture of atrophic cirrhosis. A second point of interest in the case is that it presents some features which, when viewed in connection with some of the early results of experimental work now under way in this laboratory, may furnish some definite evidence in support of the now widely accepted "toxin" theory of the etiology of so-called "acute and subacute atrophy of the liver."

Clinical History. The patient was a boy, aged six years. He was admitted to St. Vincent's Hospital, N. Y., February 27, 1914, under the care of Dr. Baner to whom, and his house physician, Dr. La Rotunda, I am indebted for the clinical data. He died July 6, 1914. In addition to the ordinary diseases of childhood, the past history reveals the fact that he had pneumonia twice, but it is not stated at what time relative to the illness for which he entered the hospital. Apart from this the child had always been in fair health until six weeks previous to admission, when his mother noticed that his abdomen protruded more than usually. She watched it daily and noticed progressive enlargement. In a short time the superficial abdominal veins became prominent and tortuous. There were three to four stools daily. The child began to lose weight and became weak and irritable. In three weeks' time paracentesis was performed and a large quantity of clear fluid obtained. The fluid rapidly reaccumulated and the diarrhea steadily increased in severity until, at the time of admission, the stools averaged seven to ten daily. Physical examination revealed marked varicosity of the veins of the abdomen and chest, ascites, and an enlarged liver with a sharply defined border extending two inches below the costal margin and a roughened, slightly nodular surface. The heart and lungs were negative. The spleen was not palpable. Results of repeated examinations of the urine were negative. Blood examinations revealed only signs of secondary anemia. Examination of the stools showed mucus, fat droplets, and fatty acid crystals with a few red cells and leukocytes. The Wassermann and von Pirquet reactions were negative. Up to the time of death the patient had been tapped thirteen times and a total of thirty-two quarts of fluid obtained.

Pathological Anatomy. An autopsy was permitted only on the abdomen and thorax. The body was that of an extremely emaciated white male child, about 125 cm. in length. The skin showed marked pallor with a faint yellowish tinge. The scleræ were faintly yellow. The abdomen was markedly distended and showed very prominent and tortuous superficial veins which coursed upward toward the intercostal spaces. There was a large quantity of clear straw-colored fluid in the peritoneal cavity and a small quantity in the serous cavities of the thorax. The heart was slightly hypertrophied but was otherwise negative. The lungs showed passive congestion and edema. The thymus gland was almost completely replaced by fat. The spleen, kidneys, stomach, and intestine showed evidence of chronic passive congestion, but were otherwise negative. There was no indication of thrombosis in the inferior vena cava.

Liver. The liver *in situ* appeared somewhat enlarged, its anterior border projecting considerably below the costal margin; but after removal it appeared smaller than normal and weighed only 630 grams, the change being due to loss of blood incident to its removal. The capsule in places was thickened and tense, while at other points it was wrinkled. The edges of the liver were fairly sharp and firm. The color of the intact organ consisted in a mottling of dark blue and reddish gray areas but after section and exposure to the air three distinct colors could be seen scattered irregularly throughout the organ—dark red, which dominated the color scheme, yellowish gray, and grayish white. The liver as a whole presented an irregularly undulating surface, in places slightly lobulated, the lobulations corresponding to the yellowish-gray areas and the depressions to the red portions. On the cut surface the yellow-gray portions appeared as elevated islands and seemed to consist of coarse columns radiating from a central vessel. Several small and medium-sized intrahepatic branches of the hepatic veins showed thrombosis. The thrombi were pink-gray in color, friable in consistency, and in places firmly attached to the vein wall.

Histology. Microscopically the yellow-gray areas consist of numerous excessively large liver lobules usually arranged around a large-sized portal canal. Occasionally there are extensive fields in which lobular structure or trabecular arrangement cannot be seen, the appearance presented being that of broad sheets of closely packed liver cells with small deeply stained nuclei which are well preserved and frequently multiple. There are no mitoses to be seen but an occasional instance of amitotic cell division can be made out. When lobular structure is recognized the lobule is seen to be considerably larger than normal. Here and there, especially near the periphery of the area, are small groups of lobules which show medium-sized areas of apparently recent central hemorrhage and necrosis. In these yellow-gray areas there is apparently no pathological change in the portal system.

The "red" areas are made up of hemorrhagic and necrotic foci alternating at regular intervals with portal canals which are, for the most part, completely stripped of liver cells. There is no blood in these portal canals, but many of them show more or less fibrosis and proliferation of bile ducts, some having lost all semblance of normal structure and being represented by nothing more than rather dense areas of young cellular connective tissue thickly interspersed with branching bile ducts. Here and there, however, are canals which have a good rim of well-preserved liver cells around them, and these, as a rule, show much less or even no proliferative change. Occasionally a number of neighboring canals are "rimmed," and then the rims appear as the peripheral portions of lobules the centers of which show hemorrhage and necrosis. These central portions are made up of free red blood cells, sometimes well preserved, sometimes disintegrated, among which are scattered here and there necrotic liver cells, a few leukocytes, and large phagocytes containing red cells or brown pigment. In many of these lobules the earliest stage of the so-called new "bile-duct" formation can be distinctly recognized. The "ducts" appear as fine epithelial strands apparently growing from the peripheral liver cells in toward the center and following closely the arrangement of liver-cell trabeculæ. Their actual continuity with the liver cells can be frequently demonstrated and an occasional connection with interlobular bile

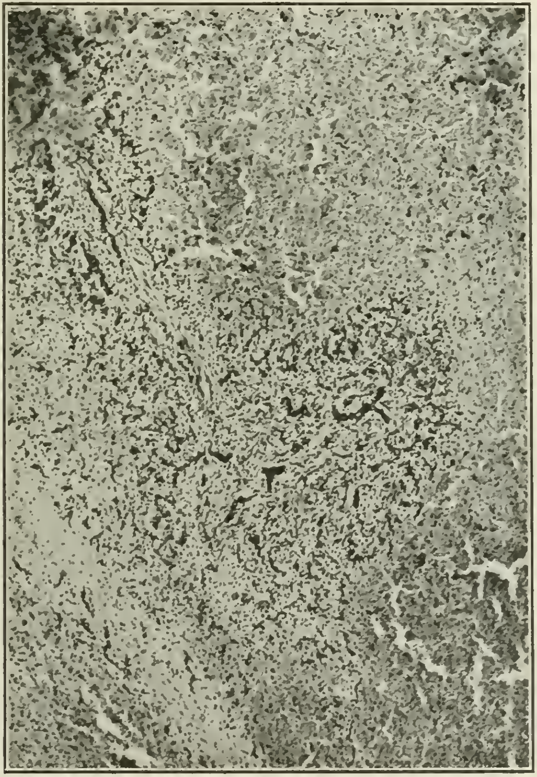

Fig. 1.—Showing portal canal with proliferating bile ducts and areas of hemorrhage and necrosis on either side.

ducts can be made out. On cross-section some of them appear to have a lumen. They are lined by fine attenuated epithelial cells with elongated highly chromatic nuclei and faintly staining cytoplasm. They show signs of vitality and proliferation that readily distinguish them from atrophying liver columns.

The "gray-white" areas are well described by terming them "duct areas." They are most numerous in the superficial portions of the liver and in the neighborhood of thrombosed hepatic veins.

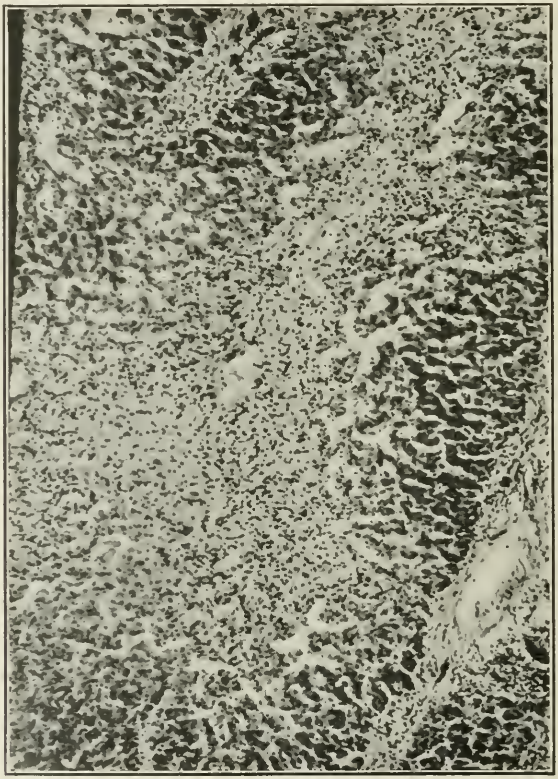

Fig. 2.—Showing central area of regenerating cells with the early formation of so-called ducts.

There is no trace of liver cells, which seem to be replaced by proliferated bile ducts rather than by fibrous tissue (Fig. 3). These branching and anastomosing ducts are thickly and evenly distributed throughout the whole of these areas, frequently forming continuous strands between the remnants of portal canals and central veins. The majority of them are lined by cuboidal epithelium and are very similar to normal bile ducts. The terminal branches, however, possess a fine attenuated epithelium and are indistinguishable from the similar formations in the "red" areas already described. The spaces between the ducts contain a large number of small irregularly shaped nuclei of an indefinite character, embedded in a homogeneous substance which takes an extremely faint stain with eosin and acid fuchsin. Some of these are probably leukocytes, some young fibroblasts, and others possibly remnants of liver cell nuclei. Collagen or elastic fibers are not demonstrable, excepting in isolated areas, representing remnants of portal canals and in the walls of bloodvessels.

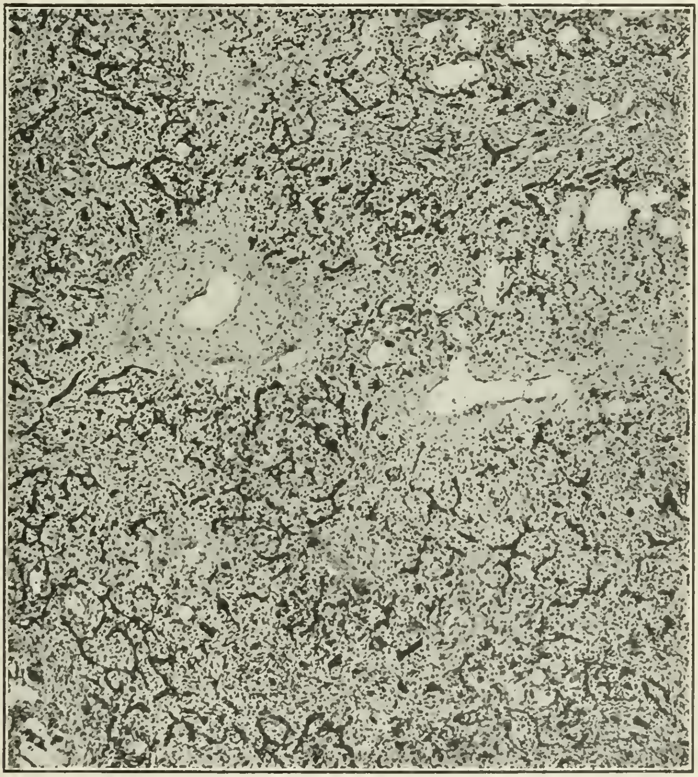

Fig. 3.—Showing a "greyish-white area" with proliferating bile ducts embedded in a moderately cellular matrix.

Perhaps the most interesting histological feature is to be found in the hepatic veins. In the hemorrhagic portions of the liver wherever central and sublobular veins can be recognized, their walls are always necrotic and in many of them are thrombi consisting of red cells and fibrin. Occasionally a thrombus is organized and canalized. The walls of the neighboring portal vessels, though possibly thickened to some extent, are always free from any signs of necrosis.

EXPERIMENTAL. I had occasion to examine for Dr. George B. Wallace, of the pharmacological department, the organs of twelve dogs and one cat injected with fatal (in twenty-four to thirty hours) doses of diphtheria toxin, and was struck with the similarity of the hepatic changes found in these animals and the early stages of those in the case above reported. I merely mention this in connection with the case under consideration in support of a "toxin" theory of its origin. In all these animals the essential changes in the liver consist of extensive central hemorrhage and necrosis, the portal canals appearing intact and surrounded by a fringe of normal liver cells. The hemorrhage is always central and usually involves the greater part of the lobule. Here and there are individual liver cells showing fragmentation or shrinkage and distortion of the nucleus. The cytoplasm stains faintly, if at all, with eosin. The walls of the capillaries and central veins are destroyed, the endothelial cells showing necrosis and desquamation. There are, however, no thrombi to be seen, either of the fibrin or of the

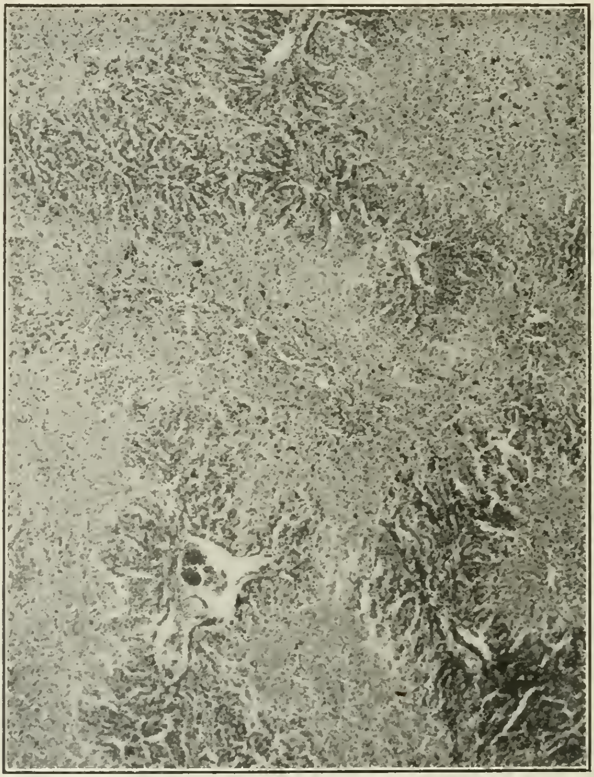

FIG. 4.—Dog's liver, showing the necrotic and hemorrhagic effects following the injection of diphtheria toxin.

agglutinated red-cell type. There is no evidence of any regenerative changes.

Necrosis of the liver similar to that found in acute yellow atrophy has been produced experimentally by Opie[3] by the combined use of chloroform and bacteria, results which could not be obtained by either one alone. Liver necroses with agglutinated red-cell thrombi were produced by Pearce[4] by the injection of hemagglutinative sera. In Pearce's cases, however, the thrombi were in the portal veins and the necroses were mostly peripheral, which is not the picture usually described in acute yellow atrophy. There is no previous case on record of the experimental production of marked central necrosis with hemorrhage by the use of bacteria alone or of bacterial toxins. Indeed, all the cases of experimental liver necroses reviewed, by whatever means produced, seem to lack the extensiveness of necrosis, the marked central hemorrhage, and the damage to the terminal hepatic veins which are so common in "acute yellow atrophy," and which are so closely imitated by the results of the injection of diphtheria toxin in animals.

SUMMARY AND SUGGESTIONS. 1. It appears not improbable that many of the cases that pass clinically for ordinary cirrhosis of the liver in children, are actually instances of subacute atrophy of the liver such as I have reported above. .

2. Histologically, the chief features in this case are extensive central hemorrhage and necrosis with marked thrombosis and necrosis of the terminal central veins, followed by replacement fibrosis together with regenerative changes.

3. I think it worthy of suggestion that the primary change is necrosis of the terminal hepatic veins, and that this was caused by the action of some bacterial toxin. What toxin this was cannot be determined. The history of the case is meagre but affirms that the patient had pneumonia twice.

4. That an exactly similar condition of necrosis of the terminal hepatic venules and capillaries with extensive central hemorrhage and necrosis can be caused by a bacterial toxin is positively demonstrated by the invariable result in the cases of the thirteen animals which were injected with diphtheria toxin. Whether the subsequent regenerative and fibrotic changes can be brought about in this way must be determined by further experimentation.

I wish to thank Dr. Douglas Symmers, in whose laboratory this study was made, for assistance. My thanks are also due to Dr. Charles Norris, of Bellevue Hospital Pathological Laboratory, for criticism and suggestions, and to Dr. George B. Wallace for the privilege of studying his experimental animals.

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ANEURYSM OF THE THORACIC AORTA: ITS INCIDENCE, DIAGNOSIS, AND PROGNOSIS. A STATISTICAL STUDY.

By Isaac Ivan Lemann, M.D.,

PROFESSOR OF CLINICAL MEDICINE, COLLEGE OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA.

(From the Pathological Department of the Charity Hospital and the Out-patient Department of Touro Infirmary.)

In two former papers I expressed my conviction that thoracic aneurysm is much more frequent than is usually thought. I desire to submit now some statistical studies which confirm this impression. The data shall also serve as a basis of discussion of incidence and diagnosis.

That the diagnosis of thoracic aneurysm is often missed is shown by the frequency in the literature of such titles as:

"A Case of Thoracic Aneurysm without Physical Findings."

"Aneurysm de la Crosse Aortique avec Absence des Signes Stethoscopique."

"Aneurysm; Absence of Physical Signs; Rupture into Primary Bronchus."

"Enormous Aneurysm of Ascending and Transverse Portions of Aortic Arch; Entire Absence of Symptoms: Death from Rupture Into Left Pleural Cavity."

"Sudden Death by Rupture of Thoracic Aneurysm Previously Unrecognized."

"A Case of Aneurysm of the Arch of the Aorta Remarkable for the Almost Total Absence of Direct Physical Signs."

Biggs[1] reports that out of 25 cases of thoracic aneurysms in which rupture occurred a history of suggestive aneurysm was presented by only 11. Draper[2] has published a similar series of ten sudden deaths by rupture of thoracic aneurysm previously unrecognized. All of which is corroborative of Osler's dictum that "there is no disease more conducive to clinical humility than aneurysm of the aorta."

The material which I have analyzed is from two sources, namely, the out-patient medical clinic of the Touro Infirmary and the autopsy records of the Charity Hospital. In the Touro clinic up to the time the analysis was made last fall (1914) 15,513 patients had been seen by my colleague, Dr. C. L. Eshleman, and myself or our assistants. In this number I have been able to find 47 thoracic aneurysms. That is to say, 0.3 per cent. (or 1 in 300) of all patients examined were found to have a thoracic aneurysm. There is no doubt that other aneurysms escaped diagnosis. These figures, extreme as they seem to be, are not as startling as the ones quoted from the Johns Hopkins Hospital by Osler in his Schorstein Lectures, namely, that in 24,363 admissions there were 204 thoracic aneurysms, 0.9 per cent. (or nearly 1 in 100). With this may also be compared the Melbourne statistics of Allen as quoted by Osler: in 46,878 admissions there were 298 aneurysms (of all arteries?). Borowsky[3] reports from the Breslau Pathological Institute 66 thoracic aneurysms in 19,646 autopsies (0.34 per cent.).

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[1] New York Med. Rec., xxxiii, 365.

[2] Sudden Death by Rupture of Thoracic Aneurysm Previously Unrecognized, Boston Med. and Surg. Jour., 1895, cxxxii, 245.

Sex and Race. In my series there were 8016 males and 7497 females. The incidence of thoracic aneurysm was as follows: males, 0.43 per cent.; females, 0.16 per cent.; in other words, thoracic aneurysm was nearly three times as frequent in males as in females. This is in accord with all previous records, and is consistent with the usually adopted theories as to etiology. If syphilis, overstrain, and alcoholism are the chief factors in the etiology, we should expect the preponderance of the male sex. On the other hand, the difference between the whites and negroes is not at all marked, contrary to my expectation and contrary to the Johns Hopkins figures already referred to. Osler says: "The ratio of colored to white in the aneurysm series is about 1 to 2.6, while the proportion of white to colored in the wards is 5 to 1." "Incidence of syphilis in the colored population is high, and many of the men have very hard work necessitating sudden effort and strain." The Touro series showed the following:

PERCENTAGE OF THORACIC ANEURYSM.

All patients	0.3
Whites, male and female	0.28
Negroes, male and female	0.34
Males, white and negro	0.43
Females, white and negro	0.16
White males	0.46
Negro males	0.49
White females	0.07
Negro females	0.22

It will be seen, therefore, that much more stress must be laid upon sex than upon race. The females were nearly one-half of the series of patients (8016 males, 7497 females), but furnish only one-quarter of the cases (12 out of 47). The white males furnished more than six times the cases that the white females did and the negro males furnished more than twice as many as the negro females. The negro female cases were relatively three times as frequent as the white female ones, while among the males the aneurysms were about as frequent in white men as in negroes. All of the above figures refer to aneurysms of the thoracic aorta. There were no abdominal aneurysms in the series of 15,513 patients. Hall[4] gives a series of 183 thoracic aneurysms admitted to the Westminster Hospital in twenty-four years; of these 160 were men and 28 women. According to Lebert the proportion is 10 men to 3 women.

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[3] Die Perforations richtung der Aneurysmen der Aorta Thoracica. Inaug. Dissert., Breslau, 1910.

Further confirmation of the frequency of aneurysm of the aorta is obtained by an analysis of the postmortem material of the Charity Hospital. In the 2000 autopsies held from August 18, 1905, to October 13, 1914, there were found 67 aneurysms of the aorta. In 33 bodies out of each thousand—3.3 per cent.—*one body in thirty* revealed an aneurysm of the aorta; 50 of these aneurysms were of the thoracic aorta and 15 were abdominal. Two bodies showed both a thoracic and an abdominal aneurysm. One body in 40—2.5 per cent.—revealed a thoracic aneurysm. These figures conform closely to those given by Osler[5] in his *Modern Medicine* article: 64 cases of aneurysm of the aorta in 2200 autopsies at Johns Hopkins Hospital—2.9 per cent. When we realize the significance of these figures, that 1 patient out of every 300 examined is found to have an aortic aneurysm, and that such a condition is found in one out of every thirty bodies opened, we shall cease to look upon aneurysm of the aorta as a rare disease.

The autopsy statistics are very much the same as those of the Touro out-patient department.

PERCENTAGE OF ANEURYSM OF AORTA.

All patients	3.3
Whites, male and female	2.9
Negroes, male and female	3.7
Males, white and negro	4.2
Females, white and negro	1.1
White males	3.4
Negro males	4.5
White females	1.1
Negro females	1.2

The percentage of the cases varies very little as between race, but very markedly as between sexes. The women are one-quarter of the total number, but furnish only one-tenth of the aneurysms. The negroes are 60 per cent. of the series and furnish 65 per cent. of the aneurysms. The percentage of aneurysms of the white females differs practically not at all from that of the negro females. The difference between the incidence in white males and negro males is somewhat more marked than in the Touro series.

The figures of thoracic aneurysm alone in the Charity Hospital postmortem series are as follows:

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[4] Lumleian Lectures on Intrathoracic Aneurysm, Lancet, London, March 22, 29 and April 5, 1913, pp. 803, 870, 945.

[5] Modern Medicine, Philadelphia, Lea & Febiger, iv, 508. Article by Osler.

PERCENTAGE OF THORACIC ANEURYSMS.

All patients	2.6
Whites, male and female	2.05
Negroes, male and female	3.04
Males, white and negro	3.2
Females, white and negro	1.0
White males	2.3
Negro males	3.2
White females	1.1
Negro females	0.9

The marked difference in the incidence in males and females is shown in every statistical study in the literature. From these I may instance the following:

		Males.	Per cent.	Females.	Per cent.
Maximoff[6] (Munich Clinic)	41 cases	29	71.2	12	28.8
Emmerich[7] (Munich Path. Inst.)	58 autopsies	39	67.2	19	32.8
Crisp	380 cases	340	89.5	40	10.5
Maximoff[8] (collected from literature)	303 "	252	84.0	51	16.0
Borowsky[9] (collected from literature)	175 "	150	85.7	25	14.3
Biggs[10] (New York coroner's inquests)	33 autopsies	25	76.0	8	24.0
Hall[11] (Westminster Hospital)	188 cases	160	85.1	28	14.1
Hall[12] (Westminster Hospital)	98 autopsies	89	90.8	9	9.2
Oswald Browne[13] (quoted by Hall)	150 "	132	88.0	18	12.0

AGE. While aneurysm of the aorta is usually a disease of middle life—from thirty-five to fifty-five years—it has been found in every age from infancy to senility. Borowsky in his collection from the literature has noted a case of a female infant, aged thirteen months, who showed at autopsy a thoracic aneurysm. Le Boutillier[14] has reported cases in children, and has gathered all the reported cases occurring in persons under twenty years of age. The oldest patient in Borowsky's report was eighty-seven years. The diagnostic lesson we must learn from this is that the possibility of a thoracic aneurysm is not to be denied in any patient on the score of age. My statistics conform closely in outline to those of other series already on record:

AGE INCIDENCE OF THORACIC ANEURYSM.

Age years.	Lemann's Touro series.	Lemann's Charity Hospital autopsy series.	Bassett-Smith.[15]	Maximoff.	Maximoff from literature.	Borowsky from literature.	Crisp quoted by Borowsky.	Emmerich, quoted by Borowsky.
1 to 10	..	..	..	..	10	1	1	
10 to 20	..	..	..	..	9	2	5	
20 to 30	1	6	13	4	28	11	71	1
30 to 40	15	17	28	4	71	43	198	7
40 to 50	19	20	6 over	14	100	58	129	16
50 to 60	8	9	..	14	56	46	65	16
60 to 70	3	3	..	5	21	10	25	11
70 to 80	..	..	..	..	5	4	8	5
Over 80	..	1	..	..	4	..	3	2
Unknown	1	10						

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[6] Beitrag zur Statistik der Aorten, Aneurysmen, Inaug. Dissert., Munich, 1910.

[7] Inaug. Dissert., Munich, 1888, quoted by Borowsky.

[8] Loc. cit. [9] Loc. cit. [10] Loc cit.

[11] Loc. cit. [12] Loc. cit. [13] Loc. cit.

[14] Case of Aneurysm of the Transverse Portion of the Aortic Arch in a Girl of Nine Years, with a Table of Reported Cases under Twenty Years Old, AMER. JOUR. MED. SCI., 1903, cxxx, 778.

[15] Brit. Med. Jour., August 31, 1907, p. 510.

Hall gives the following from autopsy records:

Age at death.	Oswald Brown's figures.	Westminster Hospital.
Under 35 years	24	21
35 to 55 "	97	71
Over 55 "	19	5
Age not given	10	1

LOCATION. I have analyzed my autopsy series also as to the location of the aneurysm. This is important not only from the point of view of accuracy and definiteness of diagnosis, but also from that of prognosis. Such a study may also serve to throw some light upon the fact that so many aneurysms run a latent course, without direct signs or symptoms. Broadbent has directed attention to the fact that aneurysms of the ascending and transverse portions of the aorta are likely to furnish physical signs, such as tumor, pulsation, thrill, bruit, etc., whereas aneurysms of the transverse and descending portions may not present any of these signs while causing by pressure symptoms such as dyspnea, dysphagia, brassy cough, change in voice, etc. Hence his classification into "aneurysms of signs" and "aneurysms of symptoms."

TABLE A.

Location.	Lemann's Charity Hospital series.		Soule[16] (quoted by Richter).	Oswald Browne St. Bartholomew', Hospital	Crisp, Lebert and Myers. (quoted by Hall).	Hall Westminster. Hospital.	Bassett-Smith.	Maximoff.	Borowsky.	Richter.
Ascending portion of thoracic aorta	8		..	58	115	28	..	7	66	8
Arch	21		15	75	113	21	29	3	43	43
Ascending and arch	1	26	..	..	..	10	..	..	25	
Arch and descending	4		..	..	..	..	8	..	..	35
Descending	9		10	17	49	18	..	2	16	
Descending thoracic and abdominal	2									
Ascending portion of the thoracic aorta and abdominal aorta	1	18	..	..	..	..	..	..	..	21
Abdominal	15		5	..	..	..	10	5		
Thoracic, location not definitely stated	6		..	..	..	6 multiple aneurysms	..	24		

It will be seen that the arch is the most usual site. Thus in my series the arch was involved in at least 38 per cent. of all aortic aneurysms and 50 per cent. of all thoracic aortic aneurysms. This latter figure may be compared with the percentages in the largest collection of thoracic aneurysms:

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[16] Summary View of Thirty Cases of Aneurysms of the Aorta from which Death Occurred in City and Country Hospitals of San Francisco, Pacific Med. and Surg. Jour., 1867, N. H., p. 9, reference; 1868, ii, 213; 1870-71, iv, 113.

	Crisp and Lebert, per cent.	Richter, per cent.	Borowsky, per cent.	
Ascending	41	10	44	
Arch	40	50	29	45
Ascending and arch			16	
Descending	19	40	10+	

Diagnosis. In turning now to a discussion of early diagnosis I do not propose to enumerate and describe all of the numerous phenomena which have been laboriously accumulated as evidence pointing to aneurysm of the thoracic aorta. Rather, I wish to emphasize the fact that if we wait for the complete classical clinical picture of thoracic aneurysm as described in our text-books, we shall miss the vast majority of cases and make a diagnosis in those instances only where the prognosis of the disease is such as to preclude any aid to the patient. I have already alluded to the well-known "latency" of the disease. That our own experience is the same as that of others is shown by the appended table of symptoms in our Touro clinic cases. In order to give these figures their full appreciation, one should remember that both Dr. Eshleman and I have been impressed by the frequency of the disease and have been keenly on the lockout for the pathognomonic signs not only before a diagnosis was made but also after the latter was established; hence when a certain phenomenon is set down as "absent" or "not mentioned" this statement should bear more weight than it would had we not been "searching" for aneurysms as it were.

INCIDENCE OF SYMPOMS: TOURO CLINIC SERIES.

	Present in cases.	Absent in cases.	Not mentionedin cases.
Bruit	20	9	18
Tracheal tug	4	16	27
Substernal dulness	33	3	11
Vertebral dulness	15	5	27
Inequality of pupils	4	25	18
Inequality of radials	5	21	21
Unequal sweating	0	0	47
Left recurrent paralysis	6	2	39
Cough	16	5	26
Pain in chest	27	..	20
Pain on pressure over sternum	4	..	43
Pain in right arm	1	..	46
Pain in left arm	7	1	39
Dysphonia	9	1	37
Dysphagia	7	1	39
Diastolic shock	4	14	39
Tumor	6	7	34
Thrill	4	12	31
Pulsation	10	1	36
Wassermann	11	9	27
Tchergunobow modification of Wassermann	10	5	22
Fluoroscope[17]	12	..	35
Roentgenogram[17]	32	1	14
History of syphilis	11	3	33

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[17] Our earlier cases were chiefly roentgen-rayed. Many of them were not fluoroscoped. Some of the later cases were examined with the fluoroscope and not roentgen-rayed.

It is noticeable that only two phenomena were present in any considerable percentage of the cases. These were pain and dulness. The importance of pain has been emphasized again and again, but the literature of recent years shows the trend to lay increasing stress upon it. Hewlett and Clark[18] name it as the main symptom, and quote approvingly from Huchard: "When one is dealing with symptoms of pain characterized by their persistency, their long duration, their intensity; when they remain unexplained, when they resist ordinary medication, finally when they present certain special characteristics, such as fixed location, or a diminished severity in certain attitudes of the patient, then we are not dealing with true neuralgia, as is too frequently assumed. In such cases one should consider aneurysm as a probable diagnosis, and if no tumor is perceptible as yet, one should turn to the roentgen rays in order to obtain certain proof." Hall gives the same advice in almost the same words. I have also been able in several of my cases to observe the characteristic attitude which Hall describes: "When he (the patient) is at ease he will sit up in bed with the knees drawn up, arms forward, shoulders slightly raised, and the head bent forward, and he will say that he breathes more comfortably in that position." The distribution of the pain I shall not go into extensively here. Suffice it to say that it may be substernal, vertebral, may extend down either arm or up the side of the neck to the occiput, as noted by Dr. Graham Steele. The pain may be continuous or may occur as typical attacks of angina. The following case from the Touro series illustrates the significance of pain:

CASE.—B. J. H., white male, aged fifty-five years, laborer, hard drinker, applied to the Touro clinic July 22, 1909, for relief of pain in the legs. Beyond an arteriosclerosis nothing abnormal was noted. After several months' treatment he was relieved of these pains. One year later (June 30, 1910) he returned, complaining of terrific pains in the left arm, beginning at the shoulder and extending down to the hand. Pressure over the brachial plexus, over the clavicle, and along the nerve trunks in the arm caused great pain. Dr. Van Wart, in consultation, suggested an intrathoracic cause for neuralgia. There were no evident symptoms of aneurysm. Percussion outline was as follows:

First intercostal space, 3½ cm. to the right of the middle line.
First intercostal space, 5½ cm. to the left of the middle line.
Second intercostal space, 4 cm. to the right of the middle line.
Second intercostal space, 4 cm. to the left of the middle line.
Third intercostal space, 4 cm. to the right of the middle line.
Third intercostal space, 8½ cm. to the left of the middle line.
Fourth intercostal space, 4 cm. to the right of the middle line.
Fourth intercostal space, 8¾ cm. to the left of the middle line.

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[18] Symptoms of Descending Thoracic Aneurysm. AM. JOUR. MED. SC., 1909, cxxxvii, 792.

Fifth intercostal space, 4 cm. to the right of the middle line.

Fifth intercostal space, 9¼ cm. to the left of the middle line.

No dulness posteriorly. Roentgenogram showed dilatation of descending arch of the aorta.

July 7, 1910. Patient spat a little blood.

September 24, 1910. Dulness was found posteriorly 6 cm. to the right of the vertebral column, extending from the first to the fourth dorsal spinous process.

Equally suggestive as pain are the disturbances of sensation, to which Head had directed attention. Hewlett and Clark and also Frick[19] have reported cases with zones on the chest wall of hyperalgesia and sometimes with anesthesia.

Physical Signs. In a previous paper[20] I have discussed the importance of percussion. In our hands it has seemed to yield earlier information of an intrathoracic growth than any other method of physical examination. The personal equation is, of course, to be taken into consideration, and each man has his hobby. Dr. Hall alludes to the fact that his series of aneurysms show a larger percentage of involvement of the recurrent laryngeal, and attributes this to the fact that he had been engaged for many years in a throat practice. A large number of cases of hoarseness would naturally come or be referred to him, and, besides, he probably included a laryngoscopic examination in his routine physical examination, which is not usual. In addition there is to be considered his greater skill in noting departures from the normal in the position of the vocal cords. I cannot, however, believe that our percussion findings are peculiar to us. The dulness was always outspoken and required no particular method nor manipulation to demonstrate. It was so often the first and only phenomenon to direct attention to intrathoracic abnormality that I am convinced that if more attention is paid to it in routine physical examinations many "latent" aneurysms will be turned to light. The abnormal dulness to which attention is called may be found in two locations. The first in the region of the manubrium. Normally percussion over the manubrium yields a note that is more resonant than that obtained over the body of the sternum, but yet not fully resonant. It is dull when compared with the percussion note in the second and first intercostal spaces to each side of the sternum. The limits of this relative dulness over the manubrium extending usually to the borders of the manubrium or just beyond, represents, I think, the outlines of the great vessels at the root of the heart, together with such other solid tissues as are normally present. When an abnormality in the anterior mediastinum exists, such as neoplasm, enlarged glands, or aneurysm the area of relative dulness is converted into one of flatness, and the conditions are reversed so that instead of the manubrium being more resonant than the body of the sternum it is duller. In addition to this the limits of the flatness (or dulness) are no longer marked by the sternal border, but extend more or less into the first and second intercostal spaces, according to the size and location of the abnormal solid mass in the mediastinum.

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[19] Nebe Objective Nachweisbare Sensibilatstörungen am Rumpfe bei Aneurysma Aorta. Wien. klin. Wchnschr., 1901, No. 25.

[20] Lemann, The Importance of Percussion in the Diagnosis of Thoracic Aneurysm, Pan-American Surgical and Medical Jour., 1914, vol. i.

The second location of abnormal dulness is over the vertebræ. Various clinicians have from time to time directed attention to percussion over the vertebræ, but it does not seem to have received the universal and routine application it deserves. Under normal conditions, percussion over the thoracic spine yields a resonant note except over the bodies of the first, second, and sometimes the third vertebræ. These are dull. Where dulness extends lower than the body of the third thoracic vertebra there exists some abnormality in the posterior mediastinum. Added significance is lent to this vertebral dulness when there is also paravertebral dulness whether on the one side or the other, but particularly on the left side. The best results are obtained when percussion is performed from below upward, that is to say, proceeding from resonance to dulness. In my Charity Hospital series are several cases in whom I observed antemortem extensive areas of dulness in the upper part of the chest posteriorly, exceeding the size of the aneurysms, large as these latter proved to be postmortem. Two of these cases I reported in my former article, and I repeat here the comment I made at that time:

"The dulness in these cases extended practically across the whole of the upper part of the back down as far as the level of the fifth or sixth thoracic spine, and over this area there was in one case for a while absolutely no respiratory sounds to be heard, and the vocal resonance was markedly diminished. I am not prepared to explain such findings beyond the suggestion that compression of the lungs may account for some of them."

ROENTGENOGRAPHY. The use of fluoroscopy and roentgenography must rank above the usual methods of physical examination on account of the greater accuracy and the sharper definition of the information secured. The roentgen rays take a subsidiary position only in that we are forced by consideration of time and economy to examine only selected cases. To the degree that we make fluoroscopic examination a routine procedure, we may expect to increase the accuracy of out diagnosis and enlarge the number of discovered "latent" aneurysms. Letulle[21] has proposed and carried out a routine which has proved most successful in this direction. He says: "If we take the trouble, as I have done in my hospital service for more than three years, to examine with the roentgen rays every chronic invalid, not only those with hypertension and the atheromatous but also all chronic nephritics, all patients with hepatic cirrhosis, tabes, chronic myocarditis, chronic bronchitis (complicated or not with bronchiectasis), and finally the lamentable cohorts of "sclereux pulmonaires," chronic lead victims and old syphilitics, we shall find innumerable diagnostic surprises. In thirty-six to forty months we have been able, my colleague, M. Anbourg and myself, to discover in this way 27 aneurysms of the aorta, all latent."[22] Lange made a comparative study of the roentgen-ray findings and the clinical histories of 19 cases in which such histories were obtainable, and was convinced "that if we wait for the appearance of the cardinal signs and symptoms as laid down in the text-books in order to make a diagnosis of aortic aneurysm, the diagnosis in many cases will be made very late and often too late to lend material aid to the patient." Baetjer[23] reports that 5 per cent. of the 104 aneurysms in his series were discovered accidentally by the roentgen rays. I think there is much common sense in Lange's[24] argument: "Musser says the roentgen rays should be resorted to in all cases of aortic aneurysm. Osler says the roentgen rays should be used in doubtful cases. But the value of the roentgen rays does not consist in confirming the presence of an aneurysm which is already indicated by one or more of its clinical signs, but the practical value of the roentgen rays to the patient lies in the recognition of small aneurysms and aortic dilatations before any cardinal signs are present." But the fact remains that it is not feasible to subject every patient to a roentgen-ray examination to make the latter a part of our routine physical examination. To adopt at least a part of Letulle's recommendation is, however, practicable and desirable. When we shall cultivate a spirit of suspicion and alertness as to obscure chest conditions and subject all such to the test of the fluoroscope we shall have made a long step in advance.

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[21] Diagnostic des Aneurismeo de l'aorte, Presse méd. 1913,, xxi, 215.

Prognosis. As to prognosis the first thing to be noted is that as our diagnostic methods improve and we come to make diagnoses earlier the prognosis will naturally improve. For if the average prognosis of any given disease be ten years while we are recognizing this disease only in an advanced stage it stands to reason that the average prognosis of the same disease even if not treated in any different way will be increased to much more than ten years if we learn to recognize it in an early instead of a late stage. A man whose aneurysm has been recognized by physician A two years earlier than by physician B will be considered by physician A to have run a two year longer course than he will be considered by physician B.

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[22] This did not include a large number of plainly manifest aneurysms diagnosed by the usual clinical methods.

[23] Johns Hopkins Hosp. Bull., 1906, xvii, 24.

[24] Some Observations on the *X*-ray Study of Twenty-five Cases of Aortic Aneurysms, Lancet-Clinic, Cincinnati, 1910, ciii, 219.

The second point of importance is that, as it is, thoracic aneurysms are of much longer duration than is usually thought. I have had several under observation for five years without observing much if any change in them. Hirsh and Robins[25] have reported one case of twenty-five years' duration substantiated by autopsy. Whipman's case lasted sixteen years and Sir W. Gardner's twelve years (both quoted by Hirsh and Robins). Lebert (quoted by Cumston[26]) gives the following table based on the time from the observation of the first symptoms until death took place:

3 months.	4 cases.
3 to 6 months.	12 cases.
12 to 15 months.	17 cases.
15 to 18 months.	10 cases.
18 to 24 months.	14 cases.
24 to 36 months.	10 cases.
36 to 48 months.	8 cases.
4 to 10 years.	9 cases.

Duration of Life of Patients with Aneurysm. Hall's experience in 35 cases in private practice was as follows: "Excluding all doubtful cases and cases in which I have not been able to trace final results, and excluding also *a patient who was alive ten years after I had made a diagnosis of aneurysm,* I find that the average duration of life works out a little over two years and eight months." There were 2 cases in which death occurred nine months after the appearance of symptoms suggestive of aneurysm and 1 *case in which death was delayed seven years.*

The third point in prognosis is that a large percentage of the cases terminate by rupture.[27] They therefore constitute an important factor in the number of sudden deaths. The patient with a thoracic aneurysm is in danger of sudden death at any time.

In my Charity Hospital series it would appear that abdominal aortic aneurysms are more prone to rupture that are thoracic aortic aneurysms. Out of 50 thoracic aneurysms 11 were reported ruptured, whereas 10 out of 17 abdominal aortic aneurysms were so reported. Upon this point I have been unable to find any additional data in the literature. The ruptures in the Charity Hospital necropsies occurred:

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[25] A Case of Aneurysm of the Aorta of Twenty-five Years' Duration, Maryland Med. Jour., 1903, xlvii, 93.

[26] The Symptomatology, Diagnosis, and Treatment of Aneurysm of the Thoracic Aorta, Arch. Diag., January, 1913.

[27] Hall gives 41 ruptures in 98 cases in one series (41 per cent.) and 8 ruptures in 35 cases in another series (23 per cent.). Browne's figures are 64 ruptures in 160 cases—42 per cent.

	Cases.
Into the esophagus	3
Into the left lung	1
Into the pericardium	2
Into the trachea	3
Into the left pleura	1
Into the right pleura	1
Total	11

According to the large tabulations of ruptures in the literature rupture externally is uncommon. More ruptures occur into the pericardium than in any other direction.

TABLE B.

Number of Cases Reported or Collected By

Ruptured into.	Borowsky.	Crisp.	Huchard.	Charcott.	Oswald Browne.	Kelynod.	Hall.	Biggs.	Total.
Pericardium	30	36	25	8	11	13	9	16	148
Left pleura	17	10	27	11	20	7	5	3	100
Right pleura	4	7	10	8	8	1	5	1	44
Trachea	16	5	17	3	3	2	2	..	48
Esophagus	15	9	6	3	7	3	6	1	50
Left bronchus	7	..	14	3	7	..	5	2	38
Right bronchus	4	..	2	1	..	1	..	..	8
Both bronchi	...	4	3	..	..	..	..	..	7
Right lung	2	3	...	..	3	..	2	..	10
Left lung	2	1	10	6	..	1	1	1	22
Left ventricle	1	1	...	..	..	..	1	..	3
Right ventricle	1	2	...	..	..	..	..	..	3
Left auricle	2	..	...	..	..	..	2	..	4
Right auricle	1	2	1	1	..	..	..	..	5
Vena cava superior	23	4	3	..	..	1	..	..	31
Vena cava inferior	1	..	...	..	..	..	..	..	1
Pulmonary artery	7	4	3	2	1	..	1	..	18
Mediastinum	4	2	4	1	..	..	..	..	11
Pericardium and right ventricle	1	..	...	..	..	..	..	..	1
Pulmonary artery and right ventricle	3	..	...	..	..	..	..	..	3
Esophagus and right bronchus	1	..	...	..	..	..	..	..	1
Subserous tissue–1	...	..	...	..	1	..	..	..	1
Externally	8	7	8	4	3	3	2	..	35
Total	150	97	133	51	64	32	41	24	592

Thus in 592 autopsies rupture occurred into the pericardium 148 times, equal to 25 per cent; externally only 35 times, equal to 5.9 per cent.

Conclusions. 1. Aneurysms of the thoracic aorta are not uncommon. Many are "latent" without direct symptoms or signs. They are a frequent cause of sudden death.

2. The first essential to their diagnosis is alertness and an attitude of suspicion in all cases of thoracic pain and of dyspnea.

3. The classical picture with typical signs and symptoms is characteristic only of far-advanced cases.

4. Of all methods of physical examination percussion (of the manubrial region, the first and second intercostal spaces and of the vertebral column) has seemed to me to yield information as to the existence of a thoracic aneurysm at the earliest date.

5. The use of the fluoroscope and the roentgen rays routinely in all cases of persistent chest pain and of dyspnea without apparent cause will reveal many latent aneurysms.

6. The early recognition of aneurysms will probably prove that the prognosis as to duration is much less unfavorable than has been hitherto thought.

AN UNUSUAL CASE OF SO-CALLED PSEUDOLEUKEMIA (LYMPHOSARCOMA).

By L. M. Warfield, M.D.,

and

H. T. Kristjanson, M.D.,

MILWAUKEE, WISCONSIN.

As a result of studies being made at the University of Wisconsin and the Milwaukee County Hospital by Bunting, Yates, and their co-workers, the conclusion is being forced upon them that Hodgkin's disease is one of the group of diseases among which are placed leukemia (lymphatic), chloroma, lymphosarcoma, pseudoleukemia, Banti's disease, mycosis fungoides, and certain forms of osteoarthritis.

We have been on the lookout for a patient showing one or more of these diseases in combination or transformation of one into the other. It was only recently that opportunity was afforded of observing a case which appeared to be typical lymphosarcoma on first admission. Upon readmission, the blood picture was that of acute lymphatic leukemia and glands removed from the axilla just before death showed a picture indistinguishable from the appearance which we believe is typical of Hodgkin's disease. The following is the history, with autopsy and bacteriological findings:

J. T., a Russian, aged twenty-five years, was admitted to the Milwaukee County Hospital September 8, 1914, complaining of swelling of glands of neck, groin, and armpits. There was nothing of moment in the family history. He had always been strong and well, and never had venereal disease. Up to two months before admission he was in good health. About that time he noticed swelling under the angle of the left jaw, followed in a short time by swelling in the left axilla and on the opposite side of the neck. Three weeks after the swellings appeared in the neck he noticed lumps in both groins. There was no pain or discomfort. Recently he had lost some weight.

On examination he was found to be a large, well-muscled man. The teeth showed some pyorrhea; the tonsils were small and hidden between the faucial pillars.

The chest, heart, and abdomen revealed nothing abnormal. On both sides of the neck, more marked on the left side, were swellings consisting of discrete hard nodules, not adherent to the skin, and not tender to pressure. On the right side several small glands were felt under the ramus of the jaw as well as in the posterior triangle of the neck. On the left side the large mass of glands was confined to the posterior triangle of the neck, with two or three small glands beneath the ramus. Similar discrete masses of glands filled both axillæ, producing visible swelling when the arms were raised above the head. In both groins were masses of glands 2 to 3 cm. in diameter.

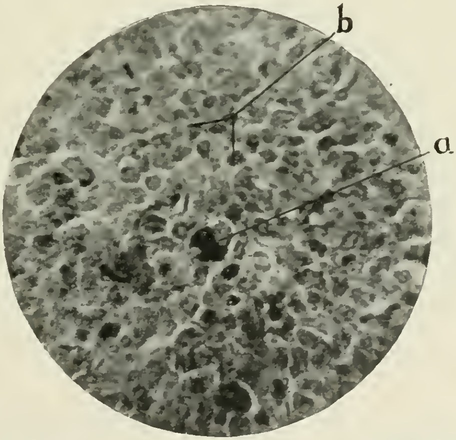

Fig. 1.—Lymph node from groin. *a*, mitotic figure; *b*, small round cells. B. L. obj. 4 mm., ocular No. 10.

The leukocytes were 9000. The average of several differential counts showed 68.8 per cent. polymorphonuclears; 22.4 per cent. small mononuclears (lymphocytes); 0.8 per cent. large lymphocytes; 5.6 per cent. transitionals; 2.0 per cent. eosinophiles; 0.4 per cent. basophiles. The platelets were not increased in number or size. Wassermann reaction was negative.

To 0.1 mg. O. T. intradermally there was a marked reaction locally, and slight constitutional reaction.

A gland removed from the groin and examined microscopically was diagnosed lymphosarcoma. Under the low power there was a dense mass of cells of uniform size (Fig. 1), taking the hematoxylin stain. When looked at with the high power the gland was seen to have lost its normal structure; there was no proliferation of stroma, the "Keimcentra" were not visible, but everywhere were cells slightly larger than those of the normal lymph gland, with small but distinct amount of protoplasm. Mitotic figures were numerous.

Coley's mixed toxin was given, beginning with ½ minim; September 23, ½ minim; 25th, 1 minim; 27th, 2 minims; October 4, 2 minims; 7th, 4 minims; 9th, 6 minims; 11th, 8 minims; 13th, 10 minims; 14th, 15 minims. There was a violent local reaction after every injection, usually a rise of temperature, but no chill. The glands did not recede, but were increasing in size.

He was then given 5 minims of Coley's toxins directly into a large gland in the right axilla. Following this injection he had a marked constitutional reaction, chill following twenty minutes after the injection, malaise. For three successive days he was given 6, 7, 8 minims into different gland groups, the last injection producing a severe constitutional reaction.

He became dissatisfied, as he was getting weaker, and left the hospital October 27. His condition was worse than it was on admission. He was readmitted November 4, 1914. He was much weaker, there was marked edema in all extremities except the left arm. The glands everywhere were much increased in size. There was edema of the scrotum and penis. There was now dulness beneath the upper part of the sternum. The abdomen was full, somewhat tense. The fulness was most marked in the epigastrium. The liver was easily palpable, the spleen was enlarged and palpable, the notch easily felt. The leukocytes numbered 112,000. A blood smear showed the typical picture of acute lymphatic leukemia. The predominating cell, 97 per cent., was a cell larger than a small mononuclear, with large single nucleus staining blue (Wright's stain) and a relatively large amount of lightly blue-staining protoplasm.

A gland was removed from the right axilla for study. That evening he seemed in no worse condition. He suddenly sank, and died early on the morning after the operation, November 11, 1914.

AUTOPSY (Dr. Kristjanson). The autopsy was performed about sixteen hours after death.

Anatomical Diagnosis. General lymphatic hyperplasia, probably lymphosarcoma; hemoperitoneum; hemothorax; edema and hypostatic congestion of lungs; chronic hyperplasia and lymphatic infiltration of spleen; chronic perisplenitis; acute parenchymatous degeneration of liver, with miliary lymphoid infiltration; cloudy swelling of kidneys, heart, adrenals; arteriosclerosis.

The body is that of a well-developed man, 163 cm. in length. Rigor mortis is very pronounced in the extremities. Slight postmortem lividity of dependent parts. Pupils unequal; right, 7 mm.; left, 5.5 mm. in diameter. The skin has a waxy appearance. Edema of lower extremities and right arm. Panniculus adiposus small in amount. In the right axilla is an incised wound 6 cm. long, neatly closed with black silk.

The cervical, axillary, inguinal, and femoral glands are greatly enlarged. They vary in size from that of a cherry to that of an English walnut, and are freely movable in the subcutaneous tissue. In the neck the lymph glands form clusters which are situated on both sides of the sternocleidomastoid muscle. The largest glands, however, are found anterior to the belly of the muscle on the left side.

Abdominal Cavity. The peritoneal cavity contains a liter or more of blood-tinged fluid, in which the intestines float free of adhesions. The peritoneum is smooth. The stomach and intestines are moderately distended. In the median line the liver projects 7 cm. below the ensiform cartilage. (The spleen was removed prior to the necropsy aseptically through a 15 cm. long incision, parallel to the left costal border, for the purpose of taking cultures.)

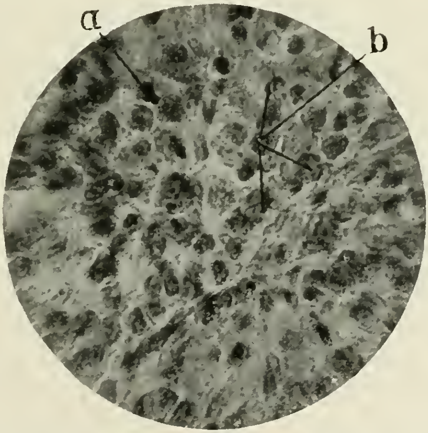

Fig. 2.—Lymph node from groin. *a*, mitotic figure; *b*, compact arrangement of cells. B. L. obj. $^1/_{12}$ oil immersion, ocular No. 10.

The mesenteric lymph nodes are enormously enlarged, forming a solid nodular mass, from which a string of greatly enlarged glands extends along the course of the iliac vessels to the internal abdominal ring. Their course is continued in the femoral region, where they can be easily palpated externally. These glands vary in size from 1.5 to 3 cm. in diameter. They are rather soft and freely movable in the adjacent tissue. Small, sessile, pea-sized nodes are irregularly scattered along the mesenteric attachment of the small intestine. Along the portal vein is noted a chain of enlarged glands, extending to the margin of the transverse fissure of the liver.

There seems to be a distinct tendency for these glands to remain discrete even after they have reached an enormous size. The smaller glands are firmer than the larger ones. All of them seem to be pretty well confined within a capsule. Generally, these glands on section have a fairly uniform consistency, are of pale gray appearance. There is no evidence of suppuration or necrosis on the cut surfaces.

Pleural Cavity. In the anterior mediastinum and at the bifurcation of the trachea are found numerous enlarged lymph nodes. The lungs nearly meet in the middle line. The left pleural cavity contains about 2 liters of bloody fluid, in which the lung floats free of adhesions. The right pleural cavity contains a small amount of bloody fluid. There are numerous rather recent adhesions between the upper lobe of the lung and the pleura.

The lobes of the right lung are bound together by old adhesions. The anterior border crepitates, the posterior is heavier, darker, and crepitates less. On section it has an excess of frothy, bloody fluid. Weight, 750 gms. The left lung weighs 650 gms. It is very similar to the right on gross appearance, except that the dark, firm area in the dependent part is smaller. The lymph nodes along the course of the main bronchi are firm and dark gray in color.

Pericardial Cavity. The pericardium is smooth, shiny, and free of adhesions. It contains about 15 c.c. of clear, yellow, serous fluid. Two or three grayish areas of connective-tissue proliferation are seen in the epicardium.

The heart weighs 280 gms. The valves appear normal. Small, slightly elevated, yellowish plaques are seen about the aortic ring and in the ascending aorta. The myocardium is brownish gray in color, fairly firm, but has generally a turbid appearance.

Thymus. The normal site of the thymus is replaced by a mass of lymphoid tissue of a very indefinite outline.

Spleen. The spleen is enormously enlarged, and weighs 1600 gms. The anterior border, which has a dull, gray, mottled appearance, lies free of adhesions. The notch is wide, and about 2 to 3 cm. deep. The omentum is united to the upper surface of the spleen by firm adhesions. The capsule is somewhat thickened. Several large, pale gray, circumscribed areas are noted over the left half of the organ. The pedicle is bound to the surrounding structures by strong adhesions. The consistency of the organ is increased. It cuts with some resistance. The cut surface reveals many irregular pale gray islands, surrounded by rather soft, reddish-brown pulp. The Malpighian corpuscles are not visible. The trabeculæ are not especially prominent, and do not seem to be increased in thickness.

Liver. The organ is greatly enlarged, weighing 3970 gms. The capsule is smooth, the color a slightly mottled grayish brown. The consistency is not increased. On section the lobules have a pale periphery, surrounded by a zone of grayish tissue. Scattered through the section are numerous opaque irregular islets a little larger than miliary tubercles. These suggest lymphoid infiltration.

Pancreas. The pancreas is large and firmer than normal. The head is buried in a cluster of lymph glands, and a chain of large glands extends along the upper border. Section shows an apparent increase in the connective tissue.

Suprarenals. These are very large. Their consistency is increased. On section, there is evident thickening of the capsule. In the cut surface there are a few small grayish circumscribed areas.

Kidneys. Together they weigh 480 gms. The left is much larger than the right. The gross appearance, however, is similar. The capsule strips readily, leaving a smooth, mottled surface. On section, the cortex is much increased, and is of an opaque granular appearance. The pyramids are rather prominent and congested.

The urinary bladder and genital organs appear normal.

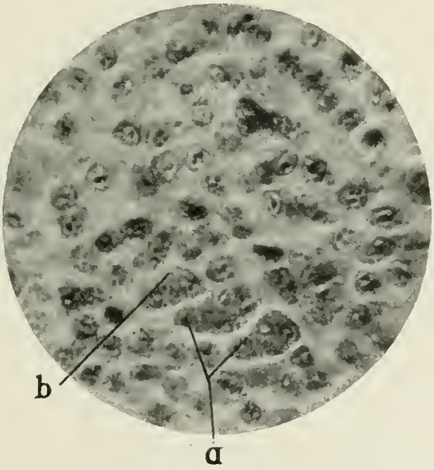

Fig. 3.—Lymph node from axilla. *a*, giant cells; *b*, endothelioid cells. B. L. obj. 4 mm., ocular No. 10.

Permission to remove the brain and spinal cord was not obtained, and unfortunately no bone marrow could be taken for study.

Microscopic Examination. The description of the gland removed from the groin has been given.

One day before death, during the time of high leukocytosis, a gland was removed from the axilla. This gland was fairly firm, on section succulent, and of a grayish color. The cut surface was glistening. The microscopic examination of this gland was most surprising. Instead of showing a uniform infiltration, with lymph cells, the cells were generally larger, were of various sizes (Fig. 3), and contained varying amounts of protoplasm. The stroma of the gland was increased, endothelioid cells were seen, and here and there a giant cell, containing several vesicular nuclei and another type, viz., deeply staining small nuclei were found. No increase in eosinophiles was seen. The gland had the appearance of what we have come to know as Hodgkin's disease.

Sections from tissues obtained at autopsy showed in all widespread cloudy swelling. No lymph nodules were seen in sections of the heart, lung, kidney, or pancreas. In the spleen the normal structure was completely destroyed. The pulp was replaced by lymph cells, fibroblasts, and plasma cells. The Malpighian bodies were not found. There was general microscopic proliferation of the stroma. The irregular islands noted on gross section were seen to be areas of more or less organized connective tissue, following upon widespread pulp necrosis. Scattered small round cells, a few eosinophiles, and fragments of nuclei of polynuclear leukocytes are seen in the new connective tissue. (Probably these necroses resulted from the injection of Coley's toxins.) Here and there are very small areas of necrosis, infiltrated with nuclear fragments. Scattered here and there are seen giant cells, for the most part situated in the lighter areas rather than in the lymph nodules.

The liver cells showed marked swelling, a granular appearance, and the columns of the lobules were widely separated. In the intercolumnar spaces were collections of lymph cells apparently in the capillaries. Here and there in the portal spaces were collections of lymph cells large enough to distort the adjacent lobules. These nodules contained not only lymph cells, but larger endothelioid cells, and an occasional giant cell.

Bacteriological Examination. Cultures from inguinal glands were made by placing pieces of the glands in tubes of Dorsett's egg medium, glycerin-phosphate-agar, and blood serum. The tubes were carefully sealed and incubated at 37° C. Four tubes out of twelve remained sterile. Five contained a pure culture of white cocci, culturally and morphologically resembling Staphylococcus pyogenes albus; the remaining tubes showed mixed growth of rapidly growing and liquefying organisms, including a few cocci.

Shortly before death implants were made from an axillary gland removed at operation, in tubes of blood serum, glycerin agar, and Dorsett's egg medium. Eighteen implantations were made. The tubes were carefully sealed. At the end of twenty days ten tubes remained sterile. Six contained a pure culture of white cocci and two showed mixed growth. In one of these tubes was noted a pleomorphic organism, strongly suggestive morphologically of a diphtheroid, but unfortunately it was outgrown before it could be isolated in a pure culture. In a similar manner, under strict aseptic precautions, twelve implantations were made, on special culture media, from the spleen six hours after death. There was no growth in nine tubes. Three tubes contained organisms that proved to be white cocci.

Bunting and Yates seem to have proved that Hodgkin's disease is a specific infection due to the B. Hodgkini. Bunting has succeeded in isolating these diphtheroids in pure culture from all of the diseases mentioned within. It would seem, therefore, that a very close relationship must exist among these diseases.

A. Fraenkel, in 1895, stated that he believed acute leukemia was an infectious disease. E. Fraenkel recently (1914) expressed the belief that there was a close relationship between lymphosarcoma and leukemia (aleukemia), but he did not think they were identical.

Oliver in a long careful criticism of the whole question of lymphosarcoma, endothelioma, and Hodgkin's disease came to the conclusion that the microscopic picture of the glands was indeed different in typical examples of these diseases, but it was altogether a matter of the part of the gland most involved. In other words, he argued for the unity of lymphosarcoma and Hodgkin's disease.

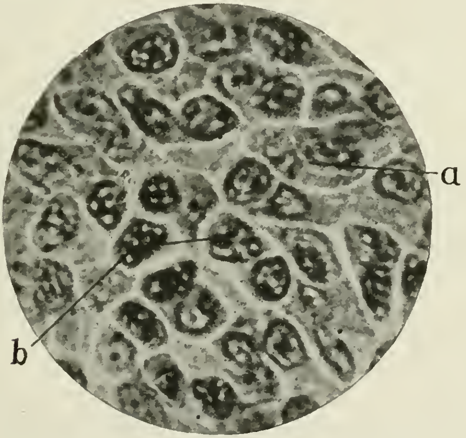

FIG. 4.—Lymph node from axilla. *a*, giant cells; *b*, endothelioid cells. B. L. obj. 1/12 oil immersion, ocular No. 10.

Craig reported a case of a man seen by him on September 18, 1901. There was a tenderness over the sternum; marked glandular enlargement everywhere; the spleen was enlarged and tender. The first blood examination showed "nothing abnormal beyond a slight leukocytosis." About one month later there were 152,000 leukocytes per cubic millimeter, nearly all of which were lymphocytes.

At the autopsy the liver was full of lymph cells, crowded in the portal spaces like lymphomata. The spleen pulp was replaced by lymph cells. The kidney glomeruli were full of lymph cells. There was a cartilaginous, yellowish-white growth beneath the sternum in the mediastinum and between the adjacent upper ribs. Microscopically the tissue was composed of reticulum and lymph cells. The diagnosis of lymphosarcoma was made.

Wende, in 1901, reported a case of a man, aged twenty-six years, who first noticed induration in the skin over the left temple five months before he was seen. The growth was rapid. Next was noticed a circumscribed hardness in the skin of the left cheek. The lymph glands in the neck rapidly enlarged, were hard and tender; first the preauricular, then the postauricular, the inferior maxillary, and the cervical. A spot in the skin near the left nipple soon appeared and rapidly increased in size. The blood was normal. A differential count showed: polymorphonuclears, 68 per cent.; small mononuclears, 27 per cent.; large lymphocytes, and transitionals, 4 per cent.; eosinophiles, 1 per cent.

There was general bronzing of the skin, thought to be due to arsenic, which had been given in large doses.

The patient had purpura and swollen gums. Three months after he was seen the leukocytes were 34,000, lymphocytes, 95.5 per cent. "The cells were of greater dimension than those of the ordinary cell." Later there was marked anemia, 45,000 leukocytes, 95.3 per cent. lymphocytes. The spleen was enlarged and the glands were everywhere increased in size. He developed an acute infection from the tonsils. The spleen and lymph glands receded markedly in size. Death occurred with symptoms of general sepsis. The pathological description resembles that of leukemia. Nowhere are there any sections which could, from the description, be called Hodgkin's disease.

We do not believe that what might be called terminal acute leukemia is so uncommon in cases diagnosed as lymphosarcoma or pseudoleukemia. By following the blood picture frequently in cases of Hodgkin's disease, Bunting has seen "the acute leukemic blood picture occur in the course of Hodgkin's disease and lymphosarcoma." This was transient. It may occur oftener than we think.

This case, we believe, lends weight to the conception of the close relationship among this group of chronic lymphatic tissue diseases.

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MEDIASTINAL LEUKOSARCOMATOSIS (STERNBERG).

By F. Parkes Weber, M.A., M.D., F.R.C.P.,
SENIOR PHYSICIAN TO THE GERMAN HOSPITAL, LONDON,
AND
F. Wolf, M.D.,
LATE HOUSE PHYSICIAN TO THE HOSPITAL.

The term "leukosarcomatosis," which was introduced by Carl Sternberg, about 1905, ought to include all tumor-like (that is to say, sarcoma-like) leukemic growths (whether the cells of the growth belong to the lymphoid or to the myeloid series) associated with or followed by leukemic changes in the circulating blood. The cases collected by Sternberg presented the features of acute or subacute leukemia associated with tumor-like formations in various positions. He regarded cases of chloroma or chlorosarcomatosis as constituting one striking type of his "leukosarcomatosis," and at the end of his paper on chloroma, published in 1905,[1] he proposed the term leukosarcomatosis (Leukosarkomatose) for the cases which were formerly regarded as a combination of leukemia and lymphosarcomatosis, and which he had elsewhere separated off as a distinct group. Cases of leukosarcomatosis other than chloroma may, in fact, be looked on as cases of chlorosarcomatosis, but without the greenish pigment from which chloroma derives its name. Among the most remarkable cases of the kind are those of "mediastinal leukosarcomatosis" in young persons, in which there is a leukemic blood picture and in which the mediastinal tumor appears to be growing from the remains of the thymus gland. In the following case and in some others, to which we shall refer later, the growth was moulded over the parietal pericardium, covering it like a blanket.

The case was that of a young man, F. K., aged eighteen years, a clerk, who was admitted to the German Hospital on March 21, 1914. The patient while in the hospital was under the care of Dr. K. Rupp, to whom our thanks are due for permission to publish this report. On admission he was fairly well nourished, and said that he had been ailing for one month and had suffered from pains in the right side. His superficial lymphatic glands on both sides of the neck, in both axillæ, and in both groins were moderately enlarged, and so were his tonsils. His spleen, which felt hard, extended downward to just below the umbilical level, and the liver was likewise somewhat enlarged. There was slight pyrexia of an irregular type. The urine was free from albumin. There was a moderate pleural effusion on the right side, and 800 c.c. of this fluid were aspirated on March 25; its specific gravity was 1008; clear; slightly red from admixture of blood.[2] A blood count on March 23 proved the case to be one of leukemia; the white cells were estimated at 131,000 to the cubic millimeter of blood. Treatment by the application of roentgen rays and the internal use of arsenic was commenced soon after the patient's admission, but the roentgen-ray therapy was discontinued after the first séance, and the case ran the invariably fatal course of acute or subacute leukemia.[3]

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[1] Carl Sternberg, Zur Kenntnis des Chloroms (Chloromyelosarkom), Beiträge zur path. Anat. und zur allg. Path., Jena, 1905, xxxvii, 437–454.

A blood examination made on March 31 gave: red cells 3,000,000 and white cells 167,500 to the cubic millimeter of blood; hemoglobin, 49 per cent. Of the white cells, 96 per cent. were lymphocytes (mostly rather large), 2 per cent. were polymorphonuclear neutrophiles, and 2 per cent. were transitionals. A few nucleated red cells were seen. The erythrocytes showed no poikilocytosis, anisocytosis, or polychromatophilia. On April 12 the right pleural effusion was again tapped and 1700 c.c. of a cloudy fluid was removed; it was of specific gravity 1015, and yielded a slightly sanguineous coagulum on standing.

In the second half of April it was obvious that the patient was going down hill and rapidly losing strength. There had been much epistaxis. There were purpuric spots (petechiæ) on the legs and retinal hemorrhages in both eyes. Since admission there had often been slight pyrexia (up to 100° F.). The lower extremities became edematous and the petechiæ gradually increased in number; dark ecchymoses appeared spontaneously about both eyes. On April 23 a fresh blood count gave 1,500,000 red cells and 176,000 white cells to the cubic millimeter of blood; nearly all the white cells were large lymphocytes, and no nucleated red cells were seen on that occasion. About that time the feces were fluid and colored red with blood. The spleen diminished somewhat in size toward the end of life, and a swelling appeared on the right side of the upper jaw (of septic dental origin?). The patient died on May 5, 1914, six and a half weeks after admission.

In regard to the nature of the mononuclear white cells (large lymphocyte type) in the present case, Dr. Gordon Ward kindly examined some blood films (of April 27) for us. He thought they were precursors of the ordinary lymphocyte type and that the leukemia was of the lymphemic type. He pointed out that there were many "Rieder cells"[4] present, but that he saw no nucleated red cells and no myelocytes such as one would expect to be present in any myeloid leukemia, even in an acute myelemia.

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[2] In cases of leukemia, pleural effusions are seldom noted during life; they are said to be always colored from admixture of blood. At the Société médicale des hôpitaux de Paris (Bull. et Mém., 1914, 3d series, xxxvii, 545), in March, 1914, Gouget and Mdlle. de Pfeffel described a case of leukemia "à forme pleurétique" in a woman, aged sixty-three years. Her illness commenced suddenly with signs of pleurisy on the right side, and she died ten days later. Her blood contained 1,302,000 red cells and 62,000 white cells to the cubic millimeter, and 68 per cent. of the white cells belonged to the "large non-granular mononuclear" class. The pleura was found sprinkled with little granules made up of the white cells.

[3] Neither roentgen-ray therapy nor arsenic nor any known form of treatment appears to be of any use in cases of acute (and subacute) leukemia.

NECROPSY. On examining the contents of the thorax a hard white tumor-like mass was seen in the superior mediastinum, apparently originating at the site of, and enclosing the remains of, the thymus gland. It spread downward over the parietal pericardium, almost the whole of which it enclosed, "like a blanket." There was some pleural effusion on the right side. The heart (weight 11 ounces), lungs, and aorta showed nothing special. The spleen was enlarged, weighing 27½ ounces and measuring 18 x 12 x 6 cm. It was of rather hard consistence and contained several anemic infarcts (doubtless of leukemic thrombotic origin), and its substance, excepting the infarcts, was of a dark crimson color. There were several perisplenitic adhesions. The liver was enlarged, weighing 80 ounces, but on section by naked-eye examination it appeared normal. The kidneys, weighing together 13 ounces, were pale. Nothing special was noted in the pancreas, alimentary canal, or thyroid gland. The brain and spinal cord were not examined. The lymphatic glands were moderately enlarged throughout; many of them were white, others were of a reddish color; among the latter were some of the mesenteric and some of the cervical glands. The right humerus was sawed open longitudinally and the marrow in the shaft was found to be of a bright red color.

MICROSCOPIC EXAMINATION. 1. *The Tumor-like Mass in the Mediastinum Enclosing the Remains of the Thymus Gland.* What remained of the thymus gland consisted of lymphoid cells with a follicular arrangement, and included a few calcified bodies, probably derived from Hassall's corpuscles. The tissue outside the capsule of the thymus gland was permeated with, and in fact consisted of, lymphoid cells of the "large lymphocyte" class, *i. e.*, of the same type as those within the capsule.

2. *A Portion of the Tumor-like Mass Outside the Remnant of the Thymus Gland.* It was found to consist chiefly of the same kind of lymphoid cells of the "large lymphocyte" class as those seen in No. 1. The tissue included scattered fat vesicles, and was evidently connective tissue densely permeated by the lymphoid cells in question.

3. *Part of the Growth from the Parietal Pericardium.* It consisted of fatty connective tissue permeated with the same kind of lymphoid cells.

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[4] "Rieder cells" or "Rieder lymphocytes" are cells of the large lymphocyte class, but with kidney-shaped or multilobed nucleus, their cytoplasm resembling that of the lymphocytes in regard to staining affinities.

4. *A Lymphatic Gland from the Left Side of the Neck.* The gland showed hyperplasia of lymphoid cells, and the surrounding connective tissue (outside the capsule of the gland) was infiltrated with the same kind of lymphoid cells.

5. *The Spleen.* Sections showed relative increase in the size of the lymph follicles (Malpighian corpuscles) and congestion of the splenic pulp between the lymph follicles. But the whole splenic substance was more or less permeated with lymphoid cells (of the same kind as those seen in the microscopic examination of the other organs). A few eosinophile cells were seen in the sections. The Prussian-blue reaction for free iron gave a negative result.

6. *The Liver.* A section of the right lobe showed great interacinous infiltration with the same kind of lymphoid cells. A section of the liver was examined for the Prussian-blue reaction (for free iron), with negative result.

7. *Kidney.* The sections showed patchy infiltration of the organ with lymphoid cells of the same type. The cells in question separated the tubules and glomeruli of the kidney without destroying them. The renal tubules appeared to have undergone extreme "cloudy swelling." The Prussian-blue reaction for free iron gave a negative result.

8. *Bone-marrow from the Shaft of the Right Humerus.* It consisted chiefly of lymphoid cells, similar to those permeating the other organs. Some of these lymphoid cells were undergoing division. There were likewise erythroblasts, and, scattered here and there, were bone-marrow giant-cells, eosinophile cells, and scanty fat vesicles.

Summing up it may be said that all the tissues examined were permeated with a kind of lymphoid cell, the mediastinal "tumor" being perhaps merely a local exaggeration of this lymphoid permeation, connected with, and apparently growing from, the remnant of the thymus gland. The conclusion was unavoidable that the lymphoid cells which permeated the various tissues of the body were of the same kind as the lymphoid cells which during the patient's life constituted by far the greatest portion of the white cells in his circulating blood. As has already been stated, these cells should probably be regarded as cells of the large lymphocyte class, or rather as "lymphoblasts," the precursors of lymphocytes, rather than as "myeloblasts," the non-granular precursors of the myelocyte series. Here it may be mentioned that the guaiac reaction with the patient's blood (tried according to the directions given in Otto Naegeli's[5] work) gave a negative result. Dr. J. S. Dunn[6] was kind enough to try the oxydase reaction for us in blood films taken during life and sections of the tissues made after the patient's death. He found that the vast majority of the mononuclear (lymphoid) cells gave no oxydase reaction, but that a few did give one, the proportion of positively reacting cells being more considerable in the kidney than in the other organs.

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[5] Blutkrankheiten und Blutdiagnostik, second German edition, Leipzig, 1912, p. 93.

[6] The Use of the Oxydase Reaction in the Differentiation of Acute Leukemias, Quarterly Journal of Medicine, Oxford, 1913, vi, 293.

Sections of the various organs stained by the Unna-Pappenheim methyl-green-pyronin method showed that the cells under discussion (of which the cell-infiltrates practically consisted) sometimes tended, according to their staining reactions, to resemble plasma cells, some of them staining almost like plasma cells, though most of them stained like "large lymphocytes." (We have to thank Dr. J. C. G. Ledingham for looking through the specially stained sections for us.)

OTHER CASES. With our present case may be compared a case of mediastinal leukosarcomatosis described by W. Mager[7] (of Brünn) in 1909. His patient was a man, aged twenty-one years, with a pleural effusion (a transudate) and enlargement of the lymphatic glands in the neck and axilla on the side of the effusion. Dilated thoracic veins, subconjunctival ecchymoses, enlargement of the spleen, and dyspnea, were notable features of the clinical picture. A blood count gave 810,000 white cells to the cubic millimeter of blood, of which 95 per cent. were large mononuclear cells of the kind found in C. Sternberg's leukosarcoma cases. The necropsy showed the presence of a large infiltrating tumor-like mass in the anterior mediastinum, consisting of characteristic cells of the same class. The illustration accompanying Mager's paper shows that the condition was very similar to that found in the case which forms the chief subject of our present communication. The main mass of the tumor was in the region of the thymus gland, but prolongations downward had grown over the parietal pericardium, enveloping it like a blanket.

Another remarkable case of mediastinal leukosarcomatosis was reported by W. D. O'Kelly[8] in 1914. The patient was a tall, slender youth, aged nineteen years. He got a severe wetting on August 13, 1913, and felt unwell after it. He then seemed weak and "remained idle." He was admitted to the hospital on September 19, 1913. The temperature was 100° F. The splenic dulness was somewhat increased. There was stomatitis. The blood serum, which had a milky appearance, gave a negative Wassermann reaction for syphilis.

Blood Examination. There were 1,472,000 red cells and 295,000 white cells to the cubic millimeter of blood; hemoglobin, 26.25 per cent. The differential count of white cells gave: polymorphonuclear neutrophiles, 1.5 per cent.; neutrophile myelocytes, 0.5 per cent.; lymphocytes, 15.5 per cent.; large mononuclears,

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[7] Zur Klinik der Leukosarkomatose, Wiener med. Wchnschr., 1909, lix, column 1877.

[8] Dublin Journal Med. Sci., 1914, cxxxvii, 409.

3.5 per cent.; myeloblasts and lymphoblasts, 79 per cent. The general condition of the patient became steadily worse, though the stomatitis disappeared. His temperature ranged between 100° and 104° F. His pulse was 100 to 140 per minute and his respiration was 24 to 36. There was slight epistaxis on October 3. Death took place on October 5, 1913. Clinically, the author pointed out, the case was one of acute leukemia of the "large lymphocyte" class, and the "leukosarcomatosis" was not discovered during life. At the postmortem examination, "on removing the sternum a large pale pink mass, the size of a closed fist, was seen filling up the superior mediastinum. It was moulded on the pericardium and the great vessels were surrounded by it. The trachea was embedded in its posterior wall. On section it was firm, with a few necrotic areas of the size of a six-penny piece. None of the usual thymic remnants were seen. . . . No pleural adhesions were present." No evidences of tuberculosis were discovered. A specimen of the blood from the heart taken at the time of the necropsy yielded a pure culture of B. coli. Microscopic examination showed the mediastinal mass to have the structure of Sternberg's leukosarcomatosis. It apparently contained no concentric corpuscles of Hassall. There was typical cellular (leukemic) infiltration of the kidneys and liver. For further details the reader must be referred to the original paper.

Another excellent illustration of mediastinal leukosarcomatosis is furnished by a specimen in the Pathological Museum of St. Bartholomew's Hospital, London, classified as "sarcoma with lymphemia" among "Diseases of the Thymus and Thyroid Glands."[9] The patient, a girl, aged five years, who died after five weeks' illness, had a blood picture of lymphocytic leukemia. The red cells were estimated at 2,000,000 per cubic millimeter of blood; the white cells numbered 60,000 per cubic millimeter, of which 88.5 per cent. were lymphocytes. At the necropsy the anterior mediastinum was found to be occupied by a large solid yellow growth, which lay upon the upper half of the pericardium and partially enveloped the lower two-thirds of the trachea. The parietal pericardium, but not the visceral pericardium, was infiltrated. The kidneys of the patient were infiltrated with yellowish secondary deposits, consisting of small round cells.

REMARKS. The above-described cases were all characterized by the presence of acute or subacute leukemia in association with a tumor-like mass in the superior mediastinum, which had spread downward over the pericardium. The following case is somewhat different. The patient, S. S., was a well-developed man, aged fifty-seven years, admitted to the hospital under one of us (F. P. W.) on May 27, 1915, with a history of having been ill for about five months. In the hospital there were general bronchitic signs, with impaired resonance at the base of the right lung; there was at one time some purulent sputum containing blood. The breathing was slightly stridulous, and there seemed to be inspiratory difficulty. There was never any fever in the hospital, but rapidly-increasing weakness was obvious. The patient died on June 9, 1915. The postmortem examination showed the presence of a large, hard, white, tumor-like mass in the mediastinum. It included, and seemed to be growing from, the pigmented bronchial glands at about the level of the bifurcation of the trachea. It enclosed the descending portion of the thoracic aorta, the lower portion of the trachea, and both bronchi, causing bronchial stenosis, the lumen of each bronchus being diminished by about half of its diameter. The growth in question infiltrated the lower part of the right lung, and a small portion of the left lung close to the left bronchus. The other organs showed no special macroscopic change, and there was no noteworthy enlargement of lymphatic glands other than the mediastinal ones. The microscopic section (for which we are greatly indebted to Dr. Hans Schmidt) showed that the mediastinal growth consisted practically entirely of round cells of the lymphocyte of lymphoblast type. Below the capsule of the kidney and in the portal spaces of the liver were small infiltrates of the same kind of round cells. It is unfortunate that no examination of the patient's blood was made, but there can hardly be any doubt that the case belonged to Sternberg's "leukosarcomatosis" group, though it differed somewhat from the preceding cases in regard to the position of the main tumor-like mass.

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[9] St. Bartholomew's Hospital Reports, London, xlii, 207, No. 2309, b. 4.

From the pathological-anatomical point of view there are, of course, besides the mediastinal group and the striking chloromatous group, several other varieties of Sternberg's "leukosarcomatosis." Cases need not necessarily be associated with obvious leukemic changes in the circulating blood, and it is permissible to speak of "aleukemic" cases when such changes are wanting. One of us has recently written on a remarkable form of leukosarcomatosis occurring chiefly in children in which the kidneys are permeated with round cells of the lymphocyte or lymphoblast type, and in which there may or may not be obvious leukemic changes in the circulating blood.[10]

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[10] F. Parkes Weber, A Note on Lymphocytomatosis or Lymphoblastomatosis, especially of the Kidneys, British Journal of Children's Diseases, London, 1915, vol. xii, 268–274.

ACUTE MYELOBLASTIC LEUKEMIA IN ITS RELATION TO PRIMARY ANEMIA.

By S. W. Sappington, M.D.,
PHILADELPHIA.

The following case is aptly illustrative of a type of blood disease in which the anemic and leukemic features compete for primary importance and invite critical comment.

Case History.—H. R., aged forty-six years, male, white, foundryman. Entered Hahnemann Hospital November 25, 1914, complaining of extreme weakness and prostration.

The family history was negative. The patient had measles in childhood and typhoid fever at twenty-one; otherwise the past history was quite negative. He had never used alcohol, tobacco, or drugs; he was never exposed to poisons such as lead or phosphorus; he strenuously denied gonorrhea and syphilis. There was no history of tuberculosis. He was married and had six children, one dying of diphtheria.

Two or three years ago the patient had considerable trouble with decaying teeth, and had all of those in the upper and part of those in the lower jaw removed. Since then he has been wearing plates. According to various members of his family, and his own physician, the patient had been distinctly and even markedly anemic for not less than six months and possibly a year. This was evidenced by a striking yellow pallor obvious to all his relatives and friends. Six weeks before entering the hospital he scraped the skin off his left arm at the wrist, and this in a few days became infected. Carbuncle-like suppuration developed and extended a short distance up the arm, but was controlled by incision and general surgical treatment, and is now completely healed. Two weeks after the arm infection, however, the patient became so weak that he had to stop work, and his physician was impressed with the rapid increase of the anemic pallor and general illness from the time of the infection. Outside of weakness and dyspnea, dizziness or faintness on effort, the case was symptomless. There was neither gain nor loss of weight. There had never been any glandular enlargement. There was no history of hemorrhage at any time or from any place, and there was no bleeding while in the hospital.

Examination. The patient was plainly seen to be extremely anemic. The marked anemic pallor with the yellowish tinge and the fairly fleshy condition of the subject suggested pernicious anemia. The mucous membranes were very pale. Along the lower incisors and bicuspids there was pyorrhea alveolaris. At a later period an ulcerated area at the junction of the natural and false teeth on the right side developed, apparently from the rubbing of the plate;

otherwise the mouth and throat had been and remained remarkably free from scorbutic, ulcerous, gangrenous, or hemorrhagic conditions.

There were no superficial or deep glandular enlargements demonstrable during his hospital stay. The spleen gave no evidence, by palpation or percussion, of increase in size.

The heart exhibited an anemic murmur. The blood-pressure was 100 mm. systolic and 50 mm. diastolic. The lungs were negative. The abdomen was negative. There was no enlargement of the liver. Examination of the gastric contents gave free HCl, 37; total acidity, 62; no lactic acid; no occult blood. The feces showed no animal parasites and no occult blood. The urine was quite negative. The Wassermann test was negative. The neurologist reported negatively, as did the ophthalmologist on the eye-grounds. Two roentgenographic examinations gave nothing definite.

The patient was twenty-five days in the hospital when he died. He complained of weakness, but otherwise was quite comfortable and mentally keen. While in the hospital he ran a temperature of from 99° to 101° F., with occasional higher flights. His pulse was 110 to 115. The blood findings are shown in tabular form. An autopsy could not be obtained.

Discussion. Ten years ago, in a suggestive article on "Acute Lymphatic Leukemia," McCrae[1] concluded: "(1) In the majority of cases of acute leukemia there is a rapid destruction of the red cells with the blood features of a severe primary anemia; (2) the essential changes in acute leukemia are in the bone-marrow; (3) in the study of future cases more attention should be paid to the changes in the red cells and the probable similarity to pernicious anemia definitely decided." He found in a review of forty cases an average color index of 0.94. In 24 out of 45 cases he found the red count below 1,500,000 and in 38 out of 45 cases below 2,500,000. He says: "Such a proportion of low counts with a high color index we find in only one other disease, namely, pernicious anemia. Does such a finding not suggest that we have with the special leukemic features also a very rapid severe anemia of the primary type?"

In studying the case herewith reported these notes of McCrae seemed especially relevant. While the red-cell findings, in acute leukemia may of themselves suggest pernicious anemia, these are, of course, at once contradicted in the very great majority of cases by a high white cell count which makes the diagnosis relatively simple. Further, glandular and splenic enlargements are common and diagnostically helpful. But glandular enlargements were absent in this patient, and with the history of chronic anemia and the blood findings of the first examination before us the diagnosis of pernicious anemia seemed justified and was made. Later the flood of the circulation with great numbers of myeloblasts had to be considered as a terminal event or a challenge to the first diagnosis.

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[1] Brit. Med. Jour., 1905, i, 404.

TABLE OF BLOOD FINDINGS.

Date of examination.	Hemoglobin, per cent.	Red cells.	Color index.	White cells.	Differential count (500 leukocytes).				Nucleated reds per c.mm.	Megaloblasts, per cent.	Normoblasts, per cent.
					Polynuclears, per cent.	Lymphocytes, per cent.	Eosinophiles, per cent.	Myeloblasts, per cent.			
Nov. 28	18	1,130,000	0.8	7,800	22.0	66.0	0.2	11.8	3,356	62	38
Dec. 5	19	820,000	1.2	12,000	32.8	30.8	0.1	36.3	3,344	56	44
Dec. 13	16	810,000	1.0	128,800	9.2	10.8	....	80.0	11,265	43	57
Dec. 14	..	....	....	132,000							
Dec. 15	..	....	....	146,000							
Dec. 16	14	865,000	0.8	163,000	9.2	3.6	....	87.2	18,267	42	58
Dec. 17	..	....	....	175,600							
Dec. 18	..	....	....	168,000							
Dec. 19	..	....	....	195,000							
Dec. 20	..	1,030,000	....	298,000	4.2	7.2	....	88.6	29,334	60	40

Note.—On the first examination were noted slight variations in the size and shape of the red cells and a fair number of macrocytes. There were slight polychromatophilia. The nucleated reds and polychromatophilia increased markedly with the progress of the disease but other red-cell changes were not as extreme. Blood plates were slightly reduced.

On November 28 the first blood findings of 1,130,000 red cells, a color index of 0.8, 7800 leukocytes, 66 per cent. of lymphocytes, and numerous nucleated reds with megaloblasts predominating appeared quite typical of pernicious anemia even though there were 11.8 per cent., of myeloblasts. Adding to this the absence of glandular and splenic enlargements and the history of chronic anemia the diagnosis seemed inevitable. In regard to the duration of the anemia I may say that while there was no previous blood examination I am reasonably sure from close questioning of four members of the family and the family physician that there was grave anemia without glandular enlargement for at least six months. The patient's appearance was such that he was the constant subject of inquiry and comment among his friends and relatives. The second blood examination, one week later, foreshadowed the myeloblastic invasion; and the third examination, fifteen days after the first, showed a full-fledged acute leukemia. Minus the leukocytic factor the blood was that of pernicious anemia; with it was that of leukemia. From December 13 until the day of his death, December 20, leukocyte counts and spreads were made daily and showed the progressive increase of myeloblasts together with the development of anemic changes in the red cells. In twelve days the white cells rose from 12,000 to 298,000.

The number of nucleated red cells was remarkable, reaching a maximum of 29,334 per cm. This is seldom seen except in a primary anemia and usually then in association with terminal leukocytic phenomena, as will be mentioned below. Megaloblasts predominated in some counts, normoblasts in others. Billings[2] reported a case somewhat similar to this in which the nucleated reds numbered 10,336 per cm., 7092 being megaloblasts. Solley[3] described a case of pernicious anemia with a normoblastic crisis, the nucleated red cells reaching 35,100. Grawitz[4] cited a grave anemia in a boy, aged seven years, the red count being 380,000 and the nucleated reds 10 per cent. of the total number. Brill[5] reported a pernicious anemia which after transfusion and splenectomy developed a blood picture also somewhat similar to my case, the nucleated red cells reaching the enormous number of 94,080 per cm.

If the case be adjudged pernicious anemia a terminal acute leukemia may be assumed. The above-mentioned cases of Billings, Grawitz, and Brill ended this way: Billings' case finally exhibited a leukocytosis of 34,000 with 29.4 per cent. of myelocytes, and looked like splenomyelogenous leukemia. Grawitz's patient had 55,000 leukocytes with 25 per cent. of myelocytes and 20 per cent. of large hyaline cells. Brill's case ended in what he terms an acute myeloid leukanemia with a white-cell count of 73,920, of which 21 per cent. were myelocytes and myeloblasts. Geissler and Japha[6] reported a terminal blood condition in a boy, aged six years, in which the red cells reached the extraordinarily low count of 158,000. The leukocytes were 34,000 with 90 per cent. of lymphocytes. Some authorities do not admit a terminal leukemia, but speak of an antemortem leukocytosis or lymphocytosis, and Grawitz considered his case pernicious anemia with leukocytosis. The case here reported, however, reaching a white cell count of 298,000 with 88.6 per cent. of large hyaline cells, not to be confused at all with lymphocytes, could hardly be classed otherwise than as a leukemia.

On the other hand the case may be considered leukemia throughout with severe terminal anemia. This would be acceptable if we were dealing with simply an acute leukemia, for most of the leukemias confused with pernicious anemia have been of this type. But this patient was certainly anemic at least six months, and the leukemia if present must have been of the chronic type. Chronic leukemias may, of course, terminate with the blood picture of the acute type. This occurred in Van der Wey's[7] and Wilkinson's[8] patients. A case of chronic myeloid leukemia I had observed for two and a half years and treated with benzol developed 54 per cent. of myeloblasts before death. Further, the low leukocyte count of the first examination is not contradictory to leukemia, for it is well known that a low count may be encountered at the beginning or end or during the course of the disease. The previous infection might explain the drop. An objection obtains here, however, which prohibits the diagnosis of chronic leukemia, and that is the entire absence of glandular or splenic enlargement. Acute leukemia may show no enlargement throughout its course, but chronic leukemias invariably present splenic or lymphatic enlargements at some time, and this patient's history is clearly contrary to this demand. Such diagnoses as aleukemia, aplastic leukemia, and atypical leukemia are likewise excluded on the same grounds, these diseases also showing splenic and glandular enlargements.

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[2] Tr. Assn. Amer. Phys., 1900, xv, 308.

[3] Reports of Presbyterian Hospital, New York, 1902, v, 189.

[4] Berl. klin. Wchnschr., 1901, xxxviii, 641.

[5] Tr. Assn. Amer. Phys., 1915, xxx.

[6] Deutsch. med. Wchnschr., 1900, xxvi, 65.

[7] Deutsch. Arch. f. klin. Med., 1896, lvii, 287.

[8] Lancet, London, 1903, i, 1739.

The term leukanemia makes a strong appeal for application here, implying as it does a combination of leukemic and anemic features. Von Leube's[9] original case had severe anemia, a relatively low leukocyte count (10,500), enlarged spleen, and a blood formula suitable for chronic leukemia. Most of the cases reported as leukanemia have been similar in these respects. The present case lacks the enlarged spleen and the usual blood formula. Moreover, the term seems to be rejected and denounced by so many hematologists that one hesitates to apply it. Ewing[10] speaks of it as a "term referring to a disease which may be regarded provisionally as constituting a point of union of leukemia and pernicious anemia." So regarded its application to this case is interesting. My patient's lesion, as far as clinical evidence could indicate, was in the bone-marrow and the predominant and diagnostic blood cell the myeloblast. The presence of large numbers of nucleated red cells and myeloblasts together with the significance of the myeloblast as a primitive parent marrow cell make its relation to pernicious anemia and leukemia suggestive.

Ward's[11] suggestion to classify leukemias as primary and secondary, just as anemias are spoken of as primary and secondary, is interesting. Such secondary leukemias have been described following sepsis and fractures. But the blood, as Ward points out, is never quite perfectly leukemic, just as the secondary hemolytic anemia is never as absolutely typical as a primary pernicious anemia. The case herewith reported might be classed as a secondary leukemia and accounted for by the preceding septic infection. Objections to this theory would be that the suppurative condition had healed about four weeks before the leukemic blood picture developed, and this blood picture was typical as far as a myeloblastic leukemia is concerned.

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[9] Berl. klin. Wchnschr., 1900, xxxvii, 851; also Deutsch. Klin., 1903, iii, 177.

[10] Clinical Pathology of the Blood, 1903, p. 484.

[11] Lancet, London, 1914, clxxxvi, 1459.

SUMMARY. A case of grave anemia presented in the last eight days of life a blood picture of acute myeloblastic leukemia with extraordinary numbers of nucleated red cells. The previous diseased blood condition, which had existed undoubtedly six months, is a question for debate, but there is much evidence to suggest it was pernicious anemia. The matter is interesting, as emphasized by McCrae, on account of the common association of severe anemia of the primary type with acute leukemia; and also because of the location of the lesion of both pernicious anemia and acute leukemia in the bone-marrow, together with the problem of the relation of the primitive myeloblast to the formation of red cells and leukocytes.

ON THE NATURE OF THE BACTERICIDAL PROPERTY OF VAGINAL SECRETION.

By Takashi Harada, M.D.,
KYOTO, JAPAN.

(From the Obstetrical Department of the Kyoto Imperial University.)

INTRODUCTION. Döderlein, in his work published in 1892, was the first investigator to make a statement in respect to the bactericidal property of vaginal secretion. During the twenty years that have elapsed since then many attempts have been made to investigate the factors causing this bactericidal property, but none of them have thus far produced any satisfactory result.

Döderlein kept the vaginal bacillus in bouillon cultures at 37° C. for one or two days, so that they might freely develop, and he produced therein a considerable amount of lactic acid. He transplanted the staphylococcus into the culture, but was unable to discover any signs of this organism, and was thus led to conclude that the lactic acid in the vagina was the product of the vaginal bacillus and was bactericidal in nature. Years after, however. Krönig discovered experimentally that lactic acid is not the product of the vaginal bacillus alone and is not by any means the sole agent possessing bactericidal power.

He obtained unsuccessful results in the treatment of cases of pathological vaginal secretion with 1 per cent. lactic acid solution, and considered this to be another evidence that the lactic acid is not sufficiently protective against the pathogenic flora therein present.

Though Winter and Witte still entertained doubts relative to the bactericidal power of vaginal secretion, its existence has been proved by several other authors (Döderlein, Bumm, Stroganoff, Krönig, Menge, etc.).

The question now to be dealt with is not in respect to the affirmation of this power, but to its real cause. Menge and Krönig experimentally demonstrated the disappearance of the Bacillus pyocyaneus after injection into the human vagina, and in the cases of streptococcus and staphylococcus they have also demonstrated its bactericidal property against these organisms.

They contradicted the statement made by Döderlein to the effect that acid alone is attributable to bactericidal property, as they found that the vaginal secretion of both neutral and alkaline reactions similarly possessed a bactericidal property. They denied, too, that the bactericidal property is due to the acidity of the vaginal secretion, in which they restated the opinion of Döderlein. They furthermore declared that the acid reaction of vaginal secretion is not caused by a bacillus, and that the aseptic vaginal secretion in children is acid, although bereft of all bactericidal property.

Stroganoff says that the bactericidal property is due to the combined acid and other effects produced by the vaginal bacillus. Briefly stated, according to Döderlein, acid is produced from the vaginal bacillus and the bactericidal property likewise proceeds from the vaginal bacillus. But my own experiments have disproved both these statements. In cultures made from the vaginal secretion only several colonies can be seen in agar or gelatin plates, and most of them are streptococci and staphylococci. Moreover, Krönig stated that the vaginal bacillus is less effective as regards bactericidal property than the bow bacillus (Bogenstäbchen).

After numerous experiments, Krönig and Menge came to the conclusion that the bactericidal property of vaginal secretion is more or less affected by the neutralizing of the acid therein contained, but that it is greatly reduced by dilutions of the vaginal secretion or by heating to a high temperature. They failed to observe the phagocytosis of the leukocytes in the vagina and experienced considerable difficulty in accounting for the reduction in the bactericidal property when the acid was neutralized. This is shown in their statement that bactericidal power is found not only in vaginal secretion, that is, in acid reaction, but also in alkaline reactions.

Several other factors are cited by them, such as the large number of the vaginal bacilli and their products, lack of oxygen in the vagina, and tissue juices. But the lack of oxygen cannot be accounted as one of the causes of the bactericidal property, as the growth of the streptococcus, which is a facultative anërobe organism, is distinctly good in regions deprived of oxygen.

Zöppritz remarked that the bactericidal power of the vaginal secretion is very effective on the streptococcus but less influential on the staphylococcus, especially on the Bacillus coli. He furthermore states that the bactericidal power of vaginal secretion is chiefly due to a factor designated by Grüber and Futaki as "leukin," combined with the actions of the vaginal bacillus and of acid. He thus asserts that it is not too much to say that no bactericidal power is participated by the action of acid. Nevertheless, according to my own experience, vaginal secretion contains as much as 0.9 per cent., which is a not insignificant quantity. We are glad that he paid special attention to leukin, but his assertion that leukin is the chief cause of bactericidal property was due to the fact that the bactericidal power of vaginal secretion suffers but little at 56° C., while it is completely removed when heated to 100° C. He would not have made this assertion had he known that the steamed vaginal secretion that, according to him, had lost its bactericidal power, gradually recovered the same.

By the above it is seen that we possess a diversity of opinion relative to the cause of the bactericidal property of vaginal secretion. The following is the result of various experiments that have been made by me in the attempt to solve this question.

I. METHODS OF EXPERIMENTATION. To begin with, the white vaginal secretion from pregnant cases (usually obtainable in quantities of only 0.05 to 0.2 c.c. from each pregnant woman) is collected into a sterile capillary pipette and diluted in from one to five or ten parts of physiological salt solution, after which 0.4 c.c. of the dilution is taken up in a test-tube. Next, one loopful of a fresh agar culture of such bacteria as are applied to test bactericidal power, namely, streptococci, staphylococci, Bacillus coli, Bacillus typhosus, etc., is put into 10 c.c. of sterilized water. After thoroughly stirring 0.05 c.c. of the mixture is taken up in a sterile capillary pipette, added to the vaginal secretion above referred to and shaken very carefully, so as to obtain a thorough mixture. It is then placed into the incubator at 37° C. for several hours, after which 0.05 c.c. is removed for agar plate culture. Next the colonies produced are counted and the strength of the bactericidal power of each sample of vaginal secretion is compared.

II. VARIATIONS IN THE BACTERICIDAL POWER OF VAGINAL SECRETION DURING THE COURSE OF PREGNANCY. All of the vaginal secretion collected in my experiments was acid in reaction and in many cases I took special care to ascertain the quantitative degree of the same. The bacteria tested were the streptococcus, staphylococcus, Bacillus coli, etc., as shown in Table I.

The result of the above experiments is to show clearly that the bactericidal power of the vaginal secretion during the course of pregnancy increases in potency with the progress of pregnancy, its climax being reached on and after the eighth month.

TABLE I.

Pregnant month.	Species of bacteria.	Dilute degree of vaginal secretion.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
			Soon.	After three hours.	After six hours.	
Third . . .	Streptococcus	10 times	5,713	3742	3072	ca $^1/_2$
Third . . .	Streptococcus	10 times	2,777	401	75	ca $^1/_{37}$
Third . . .	Streptococcus	10 times	5,713	3742	3075	ca $^1/_2$
Third . . .	Bacillus coli	10 times	15,695	5475	5250	ca $^1/_3$
		5 times	17,082	9050	2585	ca $^1/_6$
Sixth . . .	Bacillus coli	10 times	15,221	3946	2244	ca $^1/_7$
		5 times	13,464	6048	426	ca $^1/_{30}$
Seventh . .	Streptococcus	10 times	2,236	15	17	ca $^1/_{132}$
Eighth . .	Streptococcus	10 times	5,840	2628	13	ca $^1/_\infty$
Ninth . . .	Streptococcus	10 times	1,314	0	0	$^1/_\infty$
		5 times	876	0	0	$^1/_\infty$
Tenth . . .	Streptococcus	10 times	1,095	1	0	$^1/_\infty$
		5 times	1,095	1	0	$^1/_\infty$
Tenth . . .	Bacillus coli	10 times	15,375	1314	0	$^1/_\infty$
		5 times	14,388	481	0	$^1/_\infty$

TABLE II.

Pregnant month.	Species of bacteria.	Dilute degree of vaginal secretion.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
			Soon.	After three hours.	After six hours.	
Third . . .	Bacillus coli	10 times	15,695	5475	5250	ca $^1/^2$
		5 times	17,082	9050	2585	ca $^1/^6$
Sixth . . .	Bacillus coli	10 times	15,221	3946	2244	ca $^1/^7$
		5 times	13,464	6048	426	ca $^1/_{32}$
Seventh . .	Streptococcus	10 times	1,170	118	13	ca $^1/_{90}$
		5 times	1,701	58	0	$^1/_\infty$

TABLE III.

Pregnant month.	Species of bacteria.	Dilute degree of vaginal secretion.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
			Soon.	After three hours.	After six hours.	
Seventh . .	Streptococcus	10 times	2,236	15	17	ca $^1/_{132}$
Fifth . . .	Staphylococcus	5 times	890	920	31	[1]ca $^1/_{30}$
		10 times	845	204	43	[1]ca $^1/_{20}$
Sixth . . .	Bacillus coli	5 times	13,464	6048	426	ca $^1/_{31}$
		10 times	15,221	3946	2244	ca $^1/_7$
Tenth . . .	B. typhosus	5 times	1,927	204	25	[1] $^1/_{77}$
		10 times	1,890	128	63	[1] $^1/_{30}$

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[1] The secretion was heated at 56° C. for an hour.

III. Difference in the Bactericidal Power of Vaginal Secretion Varying According to the Acidity. The bactericidal power of vaginal secretion is strengthened with the increase in acidity, as appears in Table II.

IV. Difference in Bactericidal Power of Vaginal Secretion According to the Species of Bacillus. Zöppritz stated that the bactericidal power of vaginal secretion was very effective on streptococci, but not at all on staphylococci, especially the Bacillus coli. My experiments show, however, that though the bactericidal power differs according to the species of bacillus, the difference is not great. (See Table III.)

V. Qualitative and Quantitative Effect of Acid in Vaginal Secretions. I have collected vaginal secretion from over 20 pregnant cases and diluted the same in fivefold physiological salt solutions. By means of pure filtration I then examined the qualitative measures of the acid both by the method of Uhfelmann and that of Günzberg. As a result lactic acid, $C_3H_6O_3$, was produced, but no volatile fatty acid. Next, for the purpose of obtaining the acidimetry, I diluted the vaginal secretion in a fivefold solution of physiological kitchen salt. Taking 0.5 c.c. of this mixture I neutralized the same with one-tenth of normal caustic potash solution, using phenolphthalein as indicator. When it was neutralized it usually corresponded to 0.1 c.c. of $\frac{N}{10}$ KOH solution. In volume that is: $C_3H_6O_3$ = 90 molecular weight; $\frac{N}{10}$ lactic acid = 9 in one liter; 0.1 : 0.0009 :: 100 : X; X = 0.9 per cent.

Although Döderlein formerly stated that the lactic acidity of pregnant vaginal secretion is 0.4 per cent., my experiments, nevertheless, show that it contains as much as 0.9 per cent.

Furthermore, my comparisons of the lactic acidity obtained from vaginal secretions of varying periods of pregnancy showed that the degree of acidity remains unincreased as pregnancy advances as appears in Table IV.

TABLE IV.

Third . . .	a	0.15	0.11	All average quantity, 0.1.
	b	0.1		
	c	0.1		
	d	0.1		
Sixth	e . .	0.1	0.1	
Seventh . . .	f	0.1	0.115	
	g	0.13		
Tenth . . .	h	0.1	0.1	
	i	0.1		
	j	0.1		
	k	0.1		

It is thus shown that in spite of the fact that bactericidal power increases during the course of pregnancy, lactic acidity does not increase.

VI. On the Nature of the Bactericidal Power of Vaginal Secretion. (*a*) *Relation between Acid and Bactericidal Power.* Döderlein states that lactic acid is the sole agent of bactericidal power, and Stroganoff seconds his opinion. On the other hand,

TABLE V.

Species of bacteria.	Dilute degree of vaginal secretion.	Species of examining solution.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
			Soon.	After three hours.	After six hours.	
Streptococcus	5 times	Acid active solution	876	0	0	$^1/_{\infty}$
	5 times	Neutral active solution	562	10	10	$^1/_{50}$
	10 times	Acid active solution	1314	0	0	$^1/_{\infty}$
	10 times	Neutral active solution	717	2555	2774	Increase.
Streptococcus	5 times	Acid active solution	1095	1	0	$^1/_{\infty}$
	5 times	Neutral active solution	3577	174	58	$^1/_{61}$
	10 times	Acid active solution	1095	1	0	$^1/_{\infty}$
	10 times	Neutral active solution	2253	2701	2555	Increase.

TABLE VI.

Species of bacteria.	Dilute degree of vaginal secretion.	Species of examining solution.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
			Soon.	After three hours.	After six hours.	
Streptococcus	5 times	Acid inactive solution	2676	2268	1,260	ca $^1/_2$
	5 times	Neutral inactive solution	2676	3969	2,268	Increase.
	10 times	Acid inactive solution	3780	3906	2,520	ca $^1/_2$
	10 times	Neutral inactive solution	2268	3402	17,010	Increase.
Streptococcus	5 times	Acid inactive solution	3402	1134	216	ca $^1/_{15}$
	5 times	Neutral inactive solution	3969	3835	317	ca $^1/_{12}$
	10 times	Acid inactive solution	3717	693	294	$^1/_{13}$
	10 times	Neutral inactive solution	4284	2583	288	ca $^1/_{15}$

Krönig and Menge oppose the view of Döderlein, in which they are supported by Zöppritz. In order to discover the relation existing between the acid and bactericidal power of vaginal secretion I classified as follows:

(*a*) Acid active solution (sole vaginal secretion).

(*b*) Neutral active solution (vaginal secretion, neutralized with sodium carbonate or caustic potash solution.

(*c*) Acid inactive solution (vaginal secretion heated at 56° C. for one hour).

(*d*) Neutral inactive solution (vaginal secretion, which has been heated at 56° C. for one hour and neutralized).

After putting the specified bacillus into these solutions, I compared the strength of the bactericidal property, with the following results shown in Tables V and VI.

The results of these observations show that the bactericidal power of vaginal secretion is greatly reduced by the neutralization of the lactic acid contained in the vaginal secretion, but they also show that the neutralized vaginal secretion possesses still some bactericidal power. Especially upon comparing neutral inactive solutions and neutral active solutions were we led to conclude that the former especially possesses a weaker bactericidal power than the latter. From this we deduced that there are certain bactericidal substances which are destroyed at 56° C. and others which are only destroyed by the removal of the acid.

(*b*) *Bactericidal Power of Chemically Pure Lactic Acid.* As we have seen that the bactericidal power of vaginal secretion is acid, we must further examine whether chemically pure lactic acid possesses any bactericidal power or not. From the apothecary of the University I obtained 0.9 per cent. lactic acid solution, which possesses the same amount of lactic acidity as do vaginal secretions. I examined the same with the following results (see Table VII):

TABLE VII.

Species of examining solution.	Dilute degree of solution.	Species of bacteria.	Number of colony.			Proportion o either increase or decrease of bacteria after six hours.
			Soon.	After three hours.	After six hours.	
Vaginal secretion of pregnant tenth month	5 times	Streptococcus	1095	1	0	$^{1}/_{\infty}$
	10 times	Streptococcus	1095	1	0	$^{1}/_{\infty}$
Pure chemical lactic acid solution	5 times	Streptococcus	1297	100	72	ca $^{1}/_{18}$
	10 times	Streptococcus	1121	179	13	ca $^{1}/_{9}$

From the above I concluded that the lactic acidity which is contained in vaginal secretion cannot altogether account for the cause of the bactericidal property, as its power is far less than that of vaginal secretion of a ten months' pregnancy.

(*c*) *Relation between Acidity and Bactericidal Power.* By means of the above experiment I discovered that the lactic acid is not the sole agent of bactericidal power. Nevertheless, I was anxious to prove that the relation between acidity and bactericidal power is always parallel. For this purpose I collected a great deal of vaginal secretion, measuring its acidity and at the same time testing the bactericidal power of the secretion. Tables VIII and IX show the result obtained according to the acidity and the course of pregnancy:

TABLE VIII.

Pregnant month.	Quantity of acid.	Dilute degree of vaginal secretion.	Species of bacteria.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
				Soon.	After three hours.	After six hours.	
Third...	1.0	10 times	Streptococcus	2,277	401	75	ca $^1/_{37}$
Third...	0.1	10 times	Bacillus coli	15,695	5475	5250	ca $^1/_2$
		5 times	Bacillus coli	17,082	9050	2588	ca $^1/_7$
Seventh.	0.1	5 times	Bacillus coli	15,766	5584	2430	ca $^1/_6$
		10 times	Bacillus coli	15,570	6570	2628	ca $^1/_6$
Tenth ..	0.1	5 times	Bacillus coli	14,388	481	0	$^1/_\infty$
		10 times	Bacillus coli	15,373	1314	0	$^1/_\infty$
Tenth ..	0.1	5 times	Streptococcus	13,140	1	0	$^1/_\infty$
		10 times	Streptococcus	14,454	76	2	ca $^1/_\infty$

TABLE IX.

Pregnant month.	Quantity of acid.	Dilute degree of vaginal secretion.	Species of bacteria.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
				Soon.	After three hours.	After six hours.	
Third...	0.15	10 times	Streptococcus	5,713	3742	3075	ca $^1/_2$
Third...	0.1	10 times	Streptococcus	2,277	401	75	ca $^1/_{37}$
Third...	0.1	10 times	Bacillus coli	15,695	5475	5250	ca $^1/_3$
		5 times	Bacillus coli	17,082	9050	2588	ca $^1/_6$
Sixth ...	0.1	5 times	Bacillus coli	13,464	6048	426	ca $^1/_{31}$
		5 times	Bacillus coli	15,221	3946	2244	ca $^1/_7$
Seventh.	0.1	5 times	Bacillus coli	15,766	5584	2430	ca $^1/_6$
		10 times	Bacillus coli	15,570	6570	2628	ca $^1/_6$
Seventh.	0.13	10 times	Streptococcus	2,236	15	17	ca $^1/_{136}$
Tenth ..	0.1	5 times	Bacillus coli	14,388	481	0	ca $^1/_\infty$
		10 times	Bacillus coli	15,373	1314	0	$^1/_\infty$
Tenth ..	0.1	5 times	Streptococcus	13,140	1	0	$^1/_\infty$
		10 times	Streptococcus	14,454	76	2	ca $^1/_\infty$
Tenth ..	0.1	10 times	Streptococcus	13,140	7884	58	ca $^1/_{242}$

The results shown in the series of experiments led me to conclude that bactericidal power produced by lactic acid has not an absolute value; that is, although lactic acids are contained in equal quantity in vaginal secretion the bactericidal power of vaginal secretion is not unvarying, but increases during the course of pregnancy.

Thus it appears indubitable that lactic acid is not the only agent of bactericidal power, but that there exists some other factor.

(*d*) *Influence of Heat upon Bactericidal Property.* In order to test the influence of heat upon bactericidal property I heated the vaginal secretion at 56° C. for one hour (inactive solution), after which I examined the strength of the bactericidal power. (See Table X.)

TABLE X.

Pregnant month.	Species of bacteria.	Species of of vaginal secretion solution.	Dilute degree of vaginal secretion.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
				Soon.	After three hours.	After six hours.	
Third ..	Streptococcus	Inactive	5 times	2,772	6237	∞	Increase.
	Bacillus coli	Active	5 times	17,082	9050	2585	ca $^{1}/_{6}$
	Streptococcus	Inactive	10 times	2,457	∞	∞	Increase.
	Bacillus coli	Active	10 times	15,695	5475	5250	ca $^{1}/_{3}$
Fifth ...	Staphylococcus	Inactive	5 times	890	920	31	ca $^{1}/_{30}$
	Staphylococcus	Inactive	10 times	845	204	43	ca $^{1}/_{20}$
Seventh .	Streptococcus	Inactive	5 times	1,701	58	0	$^{1}/_{\infty}$
	Streptococcus	Inactive	10 times	1,170	118	13	ca $^{1}/_{90}$
	Streptococcus	Active	10 times	2,236	15	17	ca $^{1}/_{132}$
Eighth ..	Streptococcus	Inactive	5 times	2,676	2268	1260	ca $^{1}/_{2}$
	Streptococcus	Inactive	10 times	3,780	3906	2520	Decrease.
	Streptococcus	Active	10 times	5,840	2628	13	ca $^{1}/_{\infty}$
Eighth ..	Streptococcus	Inactive	5 times	2,835	452	360	ca $^{1}/_{8}$
	Streptococcus	Inactive	10 times	3,339	1701	520	ca $^{1}/_{6}$
	Streptococcus	Active	10 times	5,840	2628	13	ca $^{1}/_{\infty}$
Ninth ..	Streptococcus	Inactive	5 times	730	165	87	ca $^{1}/_{9}$
	Streptococcus	Active	5 times	876	0	0	$^{1}/_{\infty}$
	Streptococcus	Inactive	10 times	715	179	84	ca $^{1}/_{9}$
	Streptococcus	Active	10 times	1,314	0	0	$^{1}/_{\infty}$
Ninth ..	Streptococcus	Inactive	5 times	730	177	135	ca $^{1}/_{6}$
	Streptococcus	Active	5 times	876	0	0	$^{1}/_{\infty}$
Tenth ..	Streptococcus	Inactive	5 times	530	54	4	ca $^{1}/_{132}$
	Streptococcus	Active	5 times	1,095	1	0	$^{1}/_{\infty}$
	Streptococcus	Inactive	10 times	433	213	27	$^{1}/_{15}$
	Streptococcus	Active	10 times	1,095	1	0	$^{1}/_{\infty}$
Tenth ..	B. typhosus	Inactive	5 times	1,927	204	25	ca $^{1}/_{77}$
	Bacillus coli	Active	5 times	14,388	481	0	$^{1}/_{\infty}$
	B. typhosus	Inactive	10 times	1,890	128	456	ca $^{1}/_{4}$
	Bacillus coli	Active	10 times	15,373	1314	0	$^{1}/_{\infty}$

The above experiment clearly shows that although the bactericidal power of vaginal secretion is greatly affected by heating to 56° C., nevertheless it still remains present to a greater or lesser extent. The questions, What is this factor which is destroyed at 56° C.?, and What is it that withstands a temperature of 56° C.?, have not been solved.

(*e*) *Is the Bactericidal Property Caused by Association of Complement and Bacteriolysin?* From the fact that vaginal secretion of pregnant women may possess a considerable amount of dialyzed tissue juice it can easily be seen that healthy tissues or blood con-

TABLE XI.

Pregnant month.	Species of bacteria.	Dilute degree of inactive vaginal secretion.	Quantity of of inactive vaginal secretion.	Quantity of complement secretion, c.c.	Quantity of physiological salt solution, c.c.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
						Soon.	After three hours.	After six hours.	
Sixth	Streptococcus	5 times	0.4	—	—	17,739	9,198	15,111	Decrease.
	Streptococcus	5 times	0.4	0.05	—	24,304	9,198	7,488	ca $^1/_3$
	Streptococcus	10 times	0.4	—	—	21,681	14,454	14,454	ca $^1/_2$
	Streptococcus	10 times	0.4	0.05	—	19,710	11,655	8,641	ca $^1/_2$
	Streptococcus	—	—	0.05	0.4	22,188	∞	∞	Increase.
Ninth	Streptococcus	5 times	0.4	—	—	16,425	10,512	9,855	ca $^1/_{1.7}$
	Streptococcus	5 times	0.4	0.05	—	16,425	9,855	7,227	$^1/_{2.4}$
	Streptococcus	—	—	0.05	0.4	22,138	22,138	22,138	
Mixed solution	Streptococcus	5 times	0.4	0.05	—	530	54	4	ca $^1/_{130}$
	Streptococcus	5 times	0.4	0.05	—	240	20	4	ca $^1/_{60}$
	Streptococcus	10 times	0.4	—	—	433	213	27	ca $^1/_{17}$
	Streptococcus	10 times	0.4	0.05	—	484	129	29	ca $^1/_{17}$
	Streptococcus	—	—	0.05	0.4	435	194	194	ca $^1/_2$
Mixed solution	Streptococcus	5 times	0.4	—	—	730	177	135	ca $^1/_6$
	Streptococcus	5 times	0.4	0.05	—	732	187	71	ca $^1/_{10}$
	Streptococcus	—	—	0.05	0.4	435	194	194	ca $^1/_2$
Mixed solution	Streptococcus	5 times	0.4	—	—	730	165	87	ca $^1/_9$
	Streptococcus	5 times	0.4	0.05	—	491	77	27	ca $^1/_{18}$
	Streptococcus	10 times	0.4	—	—	215	179	84	ca $^1/_3$
	Streptococcus	10 times	0.4	0.05	—	220	180	91	ca $^1/_{2.5}$
	Streptococcus	—	—	0.05	0.4	435	194	271	ca $^1/_2$

tain several bactericidal substances. We must assume that these are what bacteriologists have named bacteriolysin or amboceptor. If amboceptor is the principal bactericidal substance, then it is necessary to complete its property with complement.

I therefore heated vaginal secretion at 56° C. until it had lost its complement, whereupon I added fresh blood sera thereto. Upon examination of its bactericidal property I obtained the results shown in Table XI.

This experiment shows that the addition of complement fails to render it effective; the bactericidal property of vaginal secretion is not bacteriolysin, which is necessary to complete its property with complement.

(*f*) *Are "Leukin" and "Cytase" Present?* Although it is known that bactericidal power, destroyed by heating to 56° C., cannot be reactivated by the addition of fresh complement, nevertheless when heated at 56° C. the bactericidal property possessed was seen to remain unchanged. These phenomena have been respectively designated as "cytase" by Metchnikoff and "leukin" by Gruber-Futaki. As a matter of fact, cytase is destroyed at 56° C., while leukin is not destroyed at 56° C., and both are said to be produced by the leukocytes. By microscopic examination it appears evident that the bactericidal property of vaginal secretion is produced by the leukocytes, for there are a considerable number of leukocytes and a smaller amount of detrial epithelium in vaginal secretion. Moreover, we know that leukocytes are present in greater numbers in pregnant than in non-pregnant cases and that the bactericidal power also increases with the course of pregnancy. From which we came to the conclusion that the bactericidal property of vaginal secretion is produced by the leukocytes. In order to test this experiment I first divided the vaginal secretion in two lots. By freezing one lot to −15° C., for three hours I liberated the bactericidal substance contained in the leukocytes. The second lot I left untreated. Upon comparing the two lots I obtained the results shown in Table XII.

TABLE XII.

Pregnant month.	Species of examining solution.	Dilute degree of examining solution.	Species of bacteria.	Number of colony.			Proportion of either increase or decrease of bacteria after six hours.
				Soon.	After three hours.	After six hours.	
Mixed solution	Frozen	5 times	Bacillus coli	13,140	643	200	ca $^1/_{65}$
	Not frozen	5 times	Bacillus coli	15,768	4,270	1,314	ca $^1/_{12}$
	Frozen	10 times	Bacillus coli	11,169	1,182	1,040	ca $^1/_{11}$
	Not frozen	10 times	Bacillus coli	12,483	3,613	1,620	ca $^1/_8$
Mixed solution	Frozen	5 times	Streptococcus	40,390	19,710	6,570	ca $^1/_6$
	Not frozen	5 times	Streptococcus	34,821	15,117	14,454	ca $^1/_{2.5}$
Mixed solution	Frozen	5 times	Streptococcus	8.869	97	—	ca $^1/_{92}$
	Not frozen	5 times	Streptococcus	4,202	582	—	ca $^1/_8$

By means of the above experiment I found that the frozen solution possesses a stronger bactericidal power comparatively than the unfrozen solution. And this led me to investigate why the bactericidal power became stronger when the vaginal secretion was frozen. Were the "leukin" and "cytase" produced by the leukocytes or not?

In order to elucidate this question I divided the vaginal secretion into four lots as follows:

(*a*) Vaginal secretion, frozen to −15° C. for three hours.

(*b*) Vaginal secretion, frozen to −15° C. for three hours and then heated to 56° C. for one hour.

(*c*) Vaginal secretion, heated to 56° C. for one hour.

(*d*) Vaginal secretion, left untreated.

TABLE XIII.

Species of examining solution.	Dilute degree of vaginal secretion.	Species of bacteria.	Number of colony. Soon.	Number of colony. After three hours.	Proportion of either increase or decrease of bacteria after three hours.
Vaginal secretion after three hours frozen	5 times	Streptococcus	8869	97	1/92
Vaginal secretion after three hours frozen and heated at 56° C. for an hour afterward	5 times	Streptococcus	7884	208	1/38
Original vaginal secretion	5 times	Streptococcus	4205	581	1/8
Original vaginal secretion after heated at 56° C. for an hour	5 times	Streptococcus	7300	1770	1/6

By the above experiment I found that the bactericidal substance which is contained in vaginal secretion is partly decreased by heat. It appears to me, moreover, that the bactericidal substance must be unliberated in the leukocytes, because the bactericidal property of vaginal secretion, which is first frozen and then heated, suffers a decrease of only one-third of its original property. But the fact remains that whether vaginal secretion is frozen or not the bactericidal property is certainly decreased by heat. This may be due to the decrease of the property of the substance "cytase." Furthermore, those bactericidal properties which remain, independent of the agency of heat, are the properties of "leukin" and lactic acid.

GENERAL SUMMARY. 1. The bactericidal property of pregnant vaginal secretion is not greatly affected by different bacilli.

2. The bactericidal property of pregnant vaginal secretion is gradually increased during the course of pregnancy.

3. An increase of 0.9 per cent. of lactic acid is contained in pregnant vaginal secretion.

4. The lactic acid does not increase during the course of pregnancy.

5. The bactericidal substance in pregnant vaginal secretion is not of the nature of bacteriolysin, which is completed by association with complement.

6. The bactericidal property of pregnant vaginal secretion is caused by leukin, cytase or allied substances and lactic acid.

Conclusions. By the above data I have been led to conclude that the bactericidal property of pregnant vaginal secretion is gradually increased during the course of pregnancy, but that lactic acid, which according to Döderlein and others was considered as being the sole agent of bactericidal property of vaginal secretion, suffers no increase. It is, therefore, clear that lactic acid is not only the sole agent involved. Of course, as my experiments show, the property of lactic acid is seen to be not insignificant, for it is present in the quantity of 0.9 per cent., and is possessed of bactericidal property. Therefore, it is certainly a part of the bactericidal property of vaginal secretion. Though Menge and Krönig, furthermore, stated that the bactericidal property is caused by such agents as tissue juice, lack of oxygen, the vaginal bacillus and products resulting therefrom, these statements were erroneous, as has been shown above. With regard to tissue juice, I was unable to discover whether bacteriolysin completed by the association of complement is or is not present. On the other hand, it is a fact that during pregnancy the blood stream contains a large increase of leukocytes, while the vaginal secretion in pregnancy likewise contains many leukocytes. Thus I found after several experiments that the action of the bactericidal property is caused by "leukin" and "cytase," which are both produced by the leukocytes.

Finally I came to the conclusion that the bactericidal property of pregnant vaginal secretion is more affected by leukin than by cytase and that lactic acid plays only a part of the bactericidal property.

It should, however, be remarked that we have as yet no definite proof of the existence of leukin and cytase, and we cannot, therefore, state with certainty that the bactericidal property is caused by these agents, although it is certainly caused by substances similar to them.

I take this opportunity of thanking Professor Takayama and Professor Matsushita for their kindness in directing this thesis.

A STUDY OF THE CALCIUM AND MAGNESIUM METABOLISM IN A CASE OF CHRONIC GOUT.

By Jacob Rosenbloom, M.D., Ph.D.,
PITTSBURGH.

(From the Laboratory of Dr. Jacob Rosenbloom, Pittsburgh, Pa.)

I. Introduction. Although thousands of papers have been composed dealing with the relation of metabolism of uric acid to gout,[1] practically no work has been done on the metabolism of the bases in this disease.

It is needless to point out the importance of such studies. This paper contains the results obtained in a study of the calcium and magnesium metabolism in a case of chronic gout of about fifteen years' standing.

The only papers I have found dealing with a study of the metabolism of calcium and magnesium in gout are presented below. Little[2] claimed to find an increased excretion of calcium in the urine of an acute gouty patient. His results for calcium and magnesium excretion in the urine for one day are as follows:

	CaO (gm.)	MgO (gm.)
Healthy vegetarian	0.039	0.139
Gouty patient	0.206	0.179

Mackarell, Moore, and Thomas[3] on account of finding that the majority of renal calculi are composed of calcium salts,[4] bring out evidence to show that possibly there may be some relation between calcium metabolism and gout. They also bring out the interesting fact that if there is any relation between gout and an abnormal metabolism of calcium, the present antacid therapy of gouty conditions is improper, and conclude it would be more logical to use an acid treatment on account of the fact that the calcium salts are more soluble in acid media and insoluble in alkaline media. Indeed, Joulie[5] some years ago claimed that gout was due to a retention in the blood of substances whose escape is favored not by alkalies but by acids.

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[1] For discussions of metabolism in gout see: Minkowski, Nothnagel's spez. Path. u. Ther., 1903, vol. vii. Wiener, Erg. d. Physiol., 1902, i, 555; 1903, ii, 377. Bouchard, Les mal. par ralentissement de la nutrition, 1890; Troubles prealables de la nutrition, 1900. Von Noorden, Metabolism and Practical Medicine, 1907, iii, 646. McCrudden, The Chemistry, Physiology, and Pathology of Uric Acid, 1905. Burian and Schur, Plügers Arch., 1900, lxxx, 241; 1901, lxxxvii, 239. Schittenhelm, Hand. d. Biochem., 1910, iv, 489; Die Nukleinstoffwechsel und seine Störungen, Jena, 1910.

[2] Biochem. Jour., 1907, ii, 230.

[3] Ibid., 1911, v, 161.

[4] This finding has been confirmed by the work of Kahn and Rosenbloom, Jour. Am. Med. Assn., 1912, lix, 2252; 1915, lxv, 161; Arch. Int. Med., 1913, xi, 92; Ztschr. f. exper. Path., 1914, vol. xvii.

[5] Joulie, La Medication Phosphorique, Paris, 1904.

II. METHODS. The patient received daily the following diet:

Whole milk	500 c.c.
Cream	300 c.c.
Eggs	450 grams
Horlick's malted milk	200 grams
Sugar	20 grams
Salt	6 grams
Water	2000 c.c.

This diet is purin-free and yields approximately 2830 calories, and contains about 139 gms. protein, 146 gms. fat, and 225 gms. carbohydrate.

The experimental methods were the same as those described in previous publications.[6]

III. DISCUSSION OF RESULTS. It may be noted that in the six days' study there was a retention of 0.53 gm. of calcium oxide and 0.31 gm. of magnesium oxide.

The proportions of calcium oxide[7] and magnesium oxide[8] excreted in the urine and feces is normal in quantity.

It may be concluded that the metabolism of calcium and magnesium in the case of chronic gout studied is normal in character.

TABLE I.—THE CALCIUM AND MAGNESIUM METABOLISM.

Day.	Urine.			Feces.		Intake.		Balance.	
	Volume, c.c.	Calcium oxide, gram.	Magnesium oxide, gram.	Calcium oxide, gram.	Magnesium oxide, gram.	Calcium oxide, gram.	Magnesium oxide, gram.	Calcium oxide, gram.	Magnesium oxide, gram.
1 . .	1940	0.90	0.27	1.42	0.11	2.62	0.41	+0.30	+0.03
2 . .	2220	0.93	0.28	1.42	0.11	2.34	0.47	−0.01	+0.09
3 . .	1600	0.59	0.20	1.47	0.13	2.18	0.38	+0.12	+0.05
4 . .	1700	0.75	0.18	1.47	0.13	2.22	0.34	0	+0.03
5 . .	2050	0.88	0.20	1.43	0.15	2.51	0.39	+0.20	+0.04
6 . .	2520	0.84	0.18	1.43	0.15	2.19	0.40	−0.08	+0.07

TABLE II.—PERCENTAGE EXCRETION OF CALCIUM AND MAGNESIUM IN THE URINE AND FECES.

Day.	Percentage of total calcium oxide excreted in		Percentage of total magnesium oxide excreted in	
	Urine.	Feces.	Urine.	Feces.
1 . .	38.8	61.2	71.0	29.0
2 . .	39.6	60.4	71.8	28.2
3 . .	28.6	71.4	60.6	39.4
4 . .	33.3	66.7	58.0	42.0
5 . .	38.1	61.9	57.1	42.9
6 . .	37.0	63.0	54.5	45.5

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[6] AM. JOUR. MED. SCI., 1911, cxliii, 7; 1913, cxlvi, 731; 1914, cxlviii, 65. Arch. Int. Med., 1913, xii, 276; 1914, xiv, 263.

[7] For list of ratio of the urinary and fecal calcium output in normal and pathological conditions, see Towles, AM. JOUR. MED. SC., 1910, cxl, 100.

[8] For list of ratio of the urinary and fecal magnesium output, see Renvall, Skand. Arch. f. Physiol., 1904, xvi, 94.

A CASE OF CHRONIC FAMILY JAUNDICE.

By I. H. Levy, M.D.,

ASSOCIATE PROFESSOR OF CLINICAL MEDICINE, COLLEGE OF MEDICINE,
SYRACUSE UNIVERSITY.

AND

J. L. Kantor, M.D.,

SYRACUSE, N. Y.

Case History. Miss A. H., aged twenty-four years, an office clerk, complained of her abnormal color and of severe attacks of abdominal colic. Her mother has always had jaundice, and large numbers of gall-stones were removed at operation. Her grandfather, her uncle, and her aunt, all on the mother's side, were said to have suffered from a similar condition. Her brother is apparently well.

There is nothing definite in the patient's personal or past history until she arrived at ten years of age. At that time she became "terribly" jaundiced, had fever and severe pains in the abdomen, and the abdomen increased in size. An enlargement of the liver and spleen was noted. She was confined to bed for six or seven months. Although she improved after that, her jaundice never entirely cleared up, and there were distinct exacerbations at intervals. Three years ago she had an attack of appendicitis, and her appendix and right ovary (reason not determined) were removed.

About a year ago the patient began to have attacks of pains in the epigastrium with radiation to the right shoulder. There was no nausea, but she forced herself to vomit, seeming to get some relief in this manner. She has had three severe colic attacks during this interval, the jaundice increasing after each; the urine was also observed to grow darker. The patient had no chills, but felt "clammy" during each exacerbation. She observed no regular relation between the onset of pain and the ingestion of food, but the pains seemed worse when she was nervous. There was very slight digestive disturbance, a little sour stomach lately, some regurgitation at times, and bloating. The bowels were costive. During the summer the patient had frequent nose-bleeds, but not lately. There were no symptoms (with the possible exception of slight dizziness) which could be attributed to the cardiovascular system.

Except for the occasional pains and the constant discoloration of skin the patient feels perfectly comfortable, and is happy.

Physical Examination. The patient is well developed and well nourished, active, and of a cheerful disposition. The conjunctivæ are distinctly icteric, the skin of the body moderately so, the color of the face, especially after exposure to the cold air, may be described as of a delicate tea-rose shade (icterus plus anemia).

The heart offers some points of interest. Its width by percussion at the level of the fifth space is 12 cm. This is over 46 per cent. of the total chest width at that level (normal value being $41\frac{2}{3}$ per cent.). The heart is therefore distinctly enlarged. Fluoroscopically this finding is confirmed and the organ appears to be of a "mixed" configuration. On auscultation there is a loud, rough, systolic murmur at the pulmonic area. At the junction of the fourth rib and the sternum another loud systolic murmur, softer in quality, is audible. This latter is transmitted downward toward the apex. The pulse is of good quality, 76, and regular. These findings were rather a surprise, as the patient presented no subjective evidence of cardiac involvement. Moreover, anemia could hardly be invoked to explain the entire picture. A possible congenital defect was thought of.

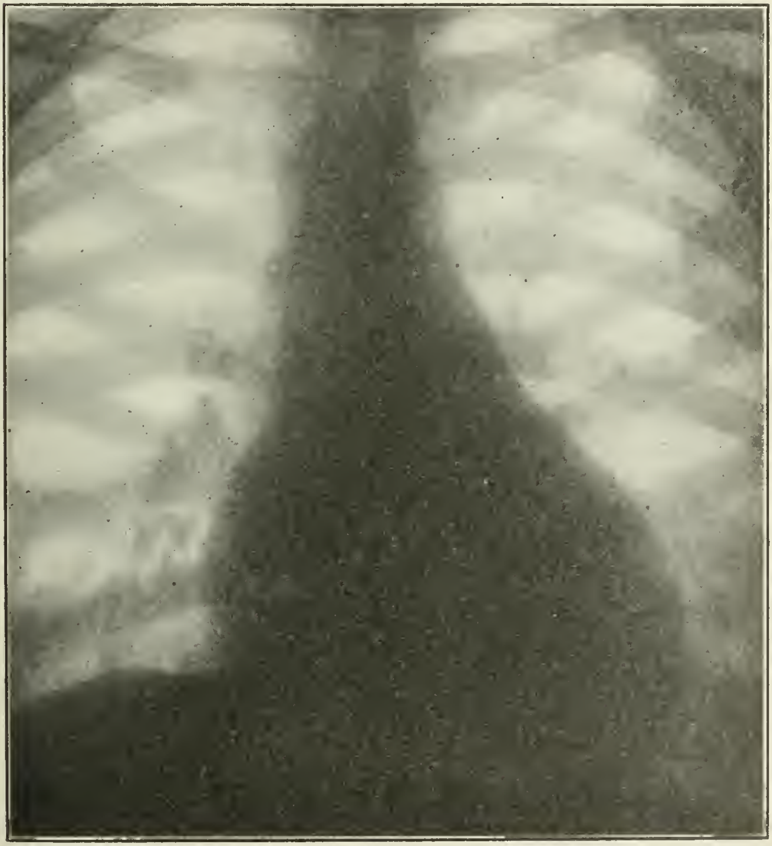

FIG. 1.—Radiograph of the heart enlarged both to right and left.

The blood-pressure was 100 mm. systolic and 55 mm. diastolic. Hypotension has apparently not been mentioned as characteristic of the disease, although most reported figures are low.

The liver edge could not be felt, but the left lobe percussed 6.5 cm. out from the spine by the Grocco method. There was tenderness at the junction of the right midclavicular line and the costal margin, as well as some resistance just below this region. The spleen was large, firm, smooth, and not tender. Its lower pole reached 8 cm. below the costal margin in the midclavicular line, its upper border to the eighth space, 13 cm. above the rib margin in the mid-axillary line, and its anterior (right) border to just within the mid-line. Its total oblique (greatest) diameter was 16 cm.

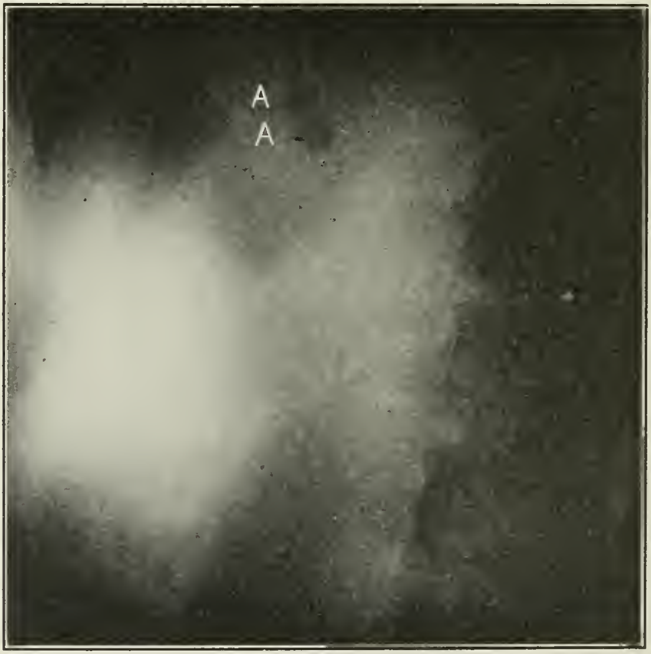

FIG. 2.—Radiograph of gall-bladder region showing two gall-stones: *A*, gall-stones.

Laboratory Findings. Blood: The coagulation time by the vein puncture method was five minutes (normal control eight minutes). The hemoglobin percentage (Sahli) was 55, 53, 65, 56 on four occasions. The total red cells numbered 2,400,000, 2,700,000, and 2,540,000, the color index being respectively 1, 1, and 0.98. Hemolysis of the erythrocytes (whole blood was used) began at 0.5 per cent. NaCl on two occasions and at 0.55 in another, the process being complete at 0.425 and 0.45 respectively. Normal bloods began to hemolyze at 0.425 and 0.45, and were completely laked at 0.325. The blood serum was positive for bile pigment (Hedenius's method). The Widal-Abrami-Brulé auto-agglutination test was negative. There was a slight though positive increase (as compared with a normal control) in the relative number of red cells showing vital staining. The size of the erythrocytes was diminished. The leukocyte counts were 3800 with 62 per cent. polynuclears and 4500 with 66 per cent. polynuclears. The Wassermann test was negative.

Urine: High colored; specific gravity 1013 to 1018; slightly acid; never bile; urobilin always present (Schlesinger test); also trace of albumin, otherwise negative.

Stool: Normal in color.

Test meal: Fasting stomach empty; Ewald meal: contents well digested, free HCl 28, total 48.

Roentgen-ray Examination. Esophagus negative, stomach vertical, fair tone, lower pole 4 inches below navel; cap normal; empty of Rieder meal within six hours. Intestines fill and empty normally.

Plate of gall-bladder region shows four small shadows, two below and two upon the same level as the twelfth rib. Shape and position characteristic of gall-stones.

DISCUSSION. The question of therapeutics is of interest in this case. At present the patient is receiving iron, is free from pain, and operative treatment is not regarded as urgent.

In their excellent study of chronic family jaundice (1910), in which they introduced the subject to American clinicians, Tileston and Griffin[1] had the following to say concerning the nature of abdominal colic in this disease:

"Attacks of abdominal pain resembling biliary colic have been observed in a large proportion of cases, and have been often supposed to be caused, in some mysterious way, by the disease itself. In two of our cases, however, gall-stones were removed at operation, after which the attacks ceased, and in both our autopsies stones were found in the gall-bladder, so that we have no hesitation in declaring that these attacks are due to gall-stones. A striking feature is the frequent onset of the colic at the time of puberty, a period at which ordinary cholelithiasis is seldom met with."

And further, under the heading of treatment they remark:

"It should be realized that attacks of abdominal pain are not due to the disease *per se*, but to a complication with gall-stones, and the patient should be given the benefit of modern surgical treatment, which has been neglected heretofore in all cases except in two of our series."

Since the above was written, evidence has been adduced tending to show that colic may be present without stones (case of Thayer and Morris[2]) in which no stones were found at operation, also two cases quoted by Elliot and Kanavel[3] and that the removal of the stones may not produce absolute relief from pain (case of Richards and Johnson[4]); relief for one year, then a mild attack). Perhaps the existence of intrahepatic calculi may explain these apparent discrepancies.

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[1] Chronic Family Jaundice, AM. JOUR. MED. SC., 1910, cxxxix, 847.

Finally, a word as to the cardiac condition. In a review of the literature from this stand-point, we found no mention of a similar condition, until we came to the report of Hichens[5] who recently presented before the Royal Society of Medicine three cases, and mentioned a fourth, of familial jaundice (in one family), each of whom showed a loud systolic murmur heard best in the third space, and transmitted upward and to the apex. This author also suggested a possible congenital origin for the condition.

Roentgenograms of the heart and stones are appended.

Since writing the above, the patient had another severe attack of gall-stone colic, and became deeply jaundiced. She was advised to have the stones removed. She entered St. Joseph's Hospital, and on January 3, 1916, Dr. Frederick Flaherty removed two fair-sized stones and a number of small ones. The ducts were free.

AUTOSEROBACTERINS.

By Michael G. Wohl, M.D.,
OMAHA, NEBRASKA.

(From the Pathological Department of the Nicholas Senn Hospital.)

In the present communication we propose to outline in brief the method of modifying sensitization of vaccines as carried out at the Nicholas Senn Hospital. A full discussion of this phase and of vaccines in general has been given in another place.[1]

Besredka,[2] in 1902, introduced sensitized vaccines into medicine. By this is meant that a suspension of bacteria (dead or alive) is mixed with serum from an immune animal and allowed to macerate

[2] Two Cases of Congenital Hemolytic Jaundice with Splenomegaly, Johns Hopkins Hosp. Bull., 1911, xxii, 85.

[3] Splenectomy for Hemolytic Icterus, Surg., Gynec. and Obstet., 1915, xxi, 21.

[4] Study of a Case of Congenital Hemolytic Jaundice, Jour. Am. Med. Assn., 1913, lxi, 1586.

[5] Cases of Familial Jaundice, Proc. Roy. Soc. Med., 1913, ix. Section of Studies of Diseases of Children, 197.

[1] Med. Record, April 29, 1916.

[2] Comp. rend. Acad. des sci., 1902, vol. c, xxxiv.

for a few hours. The serum is removed, bacteria washed and suspended in salt solution, and standardized and proper dilutions made.

The interest in sensitized vaccines is growing. Besredka himself reported 10,000 cases treated successfully with a vaccine of this kind.

Although sensitization was primarily used for typhoid vaccines, a number of men have applied the same method in other conditions. Marie[3] used it in rabies.

Meyer[4] introduced sensitized tuberculins. The *modus operandi* of sensitized vaccines can be best explained by Vaughn's theory of immunity.[5] According to Vaughn the introduction into the body of a protein sensitizer (antigen) is followed by the formation of ferments, which consist of amboceptor and complement. The ferment splits up the protein into a poisonous and non-poisonous-immunizing group. The non-poisonous group is specific and stimulates the body cells to manufacture protective substances. When bacteria are saturated with their specific antibodies by mixing them with immune serum they are ready for complete digestion by the complement with the liberation of the non-poisonous immunizing group. We owe to Bordet[6] the demonstration that the antigen with its antibody forms a complex which is "endowed with properties of absorption for complement, which neither of its constituents alone possesses." The sensitized vaccine forms, therefore, a complex which can immediately become acted upon by the complement in the body.

The method employed for sensitization, we believe, is not without its faults. The antibodies of the immune serum used for sensitization are unquestionably somewhat different from those of the patient from whom the organism is isolated for a vaccine. Rosenow[7] has given the most striking demonstration of mutation of bacteria, converting hemolytic streptococci from scarlet fever, erysipelas, etc., into streptococci and pseudopneumococci. The pneumococci, which he was able to alter culturally by special methods, were changed in regards to their reaction to agglutinins. These changes are not due to "mass action" but to active changes wrought under the influence of changed environment.[8]

If this is true then it can be easily seen how streptococci used for immunizing a horse for serum sensitization may produce antibodies (or opsonins of Wright) that vary from those of the patient. Based upon the above considerations we therefore think it not illogical to employ the patient's own serum for sensitizing the autogenous vaccines. (A somewhat similar though independent procedure is being used at the Murphy clinics.)[9]

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[3] Interstate Med. Jour., 1914, vol. xxi, 5.

[4] Infection and Resistance, McMillan Co., New York, 1914, p. 357.

[5] Vaughn-Protein Split Products, Lea & Febiger, Philadelphia, 1913; Vaughn, Reply to Stewart, New York Med. Jour., February 14, 1914, p. 324.

[6] Studies in Immunity, Gay Wiley & Sons, New York, 1909, cited by Zinsser, Infection and Resistance.

[7] Jour. Infec. Dis., 1914, xiv, 1.

[8] Vaughn, Jour. Lab. and Clin. Med., November, 1915, p. 145.

Another rather technical point is the freeing of the bacteria from the serum. During the process of washing the bacteria one is apt to disunite the antibodies from the vaccine, thus failing to accomplish the desired end.

From the studies of Eisenburg and Volk,[10] we know the complete absorption of the antibodies by the antigen is impossible, and even when absorption is done repeatedly the antibodies remain in the serum. Now, by removing the serum we discard some antibodies, which may be of importance in raising the resistance of the patient. Therefore, we believe it rational not to remove serum from vaccines after sensitization, but to use the serum plus the vaccine.

The use of the mixture of the serum and vaccine has been employed by Lorenz,[11] in hog erysipelas, and in plague by Calmette and Salimbeni.[12]

Friedberger[13] believes that immune serum after sensitization exhibits an inhibitory effect. However, this was not the case with our patients. On the contrary, they have shown no ill effects, and our therapeutic results obtained were quicker and of higher degree.

This is in accord with Theobald Smith,[14] and Park and Zingher[15] who have shown that when diphtheria-toxin antitoxin is administrated the immunity that results is of higher degree. Our technic for the preparation of autosensitized vaccines is as follows:

1. A pure culture is obtained from the lesion on solid medium. Three ordinary culture tubes are sufficient.

2. To each tube 1 c.c. of sterile normal salt solution is added. Shake the fluid so as to bring the microörganisms in suspension. To facilitate the washing off of the bacteria, use a platinum loop.

3. Transfer the bacterial emulsion into a sterile tube to which sterile glass beads are added to break up the clumps.

4. The bacterial emulsion is standardized by Wright's method of counting the proportion of red corpuscles and bacteria in the unit of equal parts of blood and bacterial emulsion, and proper dilutions are prepared. (We found that dilutions made according to the cloudiness of the bacterial emulsion answers all clinical purposes.)

5. The vaccines are now sterilized in a water-bath at 56° to 58° C. for thirty to forty-five minutes.

6. Blood is obtained from the patient from a prominent vein at the elbow. (5 to 10 c.c.) Strict attention should be paid to asepsis.

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[9] Murphy's Clinics, December, 1914, p. 1120.

[10] Ztschr. f. Hyg., 1902, vol. xl; Centralbl. f. Bact., 1903, vol. xxxiv.

[11] Interstate Med. Jour., 1914, vol. xxi, No. v.

[12] Annals de l'institut Pasteur, 1899.

[13] Berlin, klin. Wchnschr., 1902, No. 25.

[14] Jour. Am. Med. Assn., 1913, vol. lx, No. 21.

[15] Ibid., December 25, 1915.

Blood is placed in cold place for three hours and serum pipetted off.[16]

7. Inactivate the serum at 56° C. for half hour.

8. Add from 1 to 3 c.c. of the inactivated serum to vaccine No. 1, and No. 2, if enough serum is obtained, and place in incubator at 37° C. for six hours. For subsequent doses obtain more blood.

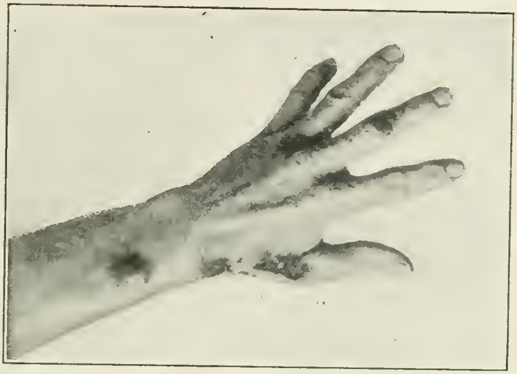

Fig. 1.—Mr. R. Left hand before treatment. Note the boils.

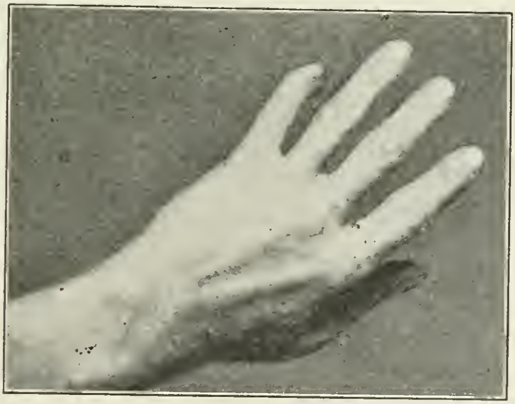

Fig. 2.—Left hand after treatment with autoserobacterins.

9. Culture vaccine to test sterility and if it is found sterile, administer it hypodermically.

If strict aseptic precautions are taken and unnecessary handling of the serum is avoided, contamination is rather an infrequent occurrence. The cases in which we have employed the sensitized vaccines are:

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[16] About 0.05 c.c. of serum is placed aside for agglutination reaction with part of the non-sterilized bacterial suspension. If the patient's serum contains agglutinins in dilutions above 1 to 10 step 7 is followed. Should the agglutinin content be too low two or three doses of the simple autogenous vaccine are administered and then blood withdrawn for sensitization.

Furunculosis	6
Cystitis (colon)	1
Erysipelas	1
Acne vulgaris	2
Otitis media, subacute	3
Infection of compound fracture	1
Gonorrheal vaginitis	2
Puerperal fever	1
(Streptotocci isolated from blood and on account of anemic condition of patient, we used commercial antistreptococcic serum for sensitization.)	
Rabies (blood taken after ten doses of antirabic vaccine administered)	1

The above-treated cases have greatly improved. The treatment is continued for six to ten doses at five-day intervals. (Some greatly improved after four doses, so that treatment was discontinued.) During the treatment the patient showed no constitutional reaction. The local reaction in most of the cases consisted in a redness the size of a dime to half dollar; induration slight; it usually disappeared at the end of forty-eight hours.

Although our cases are too few to warrant any conclusions, yet our results were so gratifying that we wish to advocate their wider application.

Conclusions. 1. Sensitized vaccines are superior to unsensitized.

2. The use of the patient's own serum for sensitization is scientifically justified.

3. The use of the serum and sensitized vaccines is based upon scientific data, and clinically is proving of great value.

REVIEWS

OBSTETRICS. A PRACTICAL TEXT-BOOK FOR STUDENTS AND PRACTITIONERS. By EDWIN BRADFORD CRAGIN, M.D., Professor of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, New York. Assisted by GEORGE H. RYLER, M.D., Instructor in Gynecology, College of Physicians and Surgeons, Columbia University, New York. Pp. 858; illustrated with 499 engravings and 13 plates. Philadelphia and New York: Lea & Febiger, 1916.

IN the preface the author states that he has written this book from a sense of duty, to place before the profession and students of medicine the methods of the Sloane Hospital for Women, and the results obtained. He also desires to present for the study of the profession American statistics in obstetrics. He believes that many books before the profession are too large for the under-graduate students, and so he has confined himself to a volume of 858 pages.

The first part of the volume is devoted to anatomy and embryology, and the anatomical descriptions are good, and many of the illustrations, notably those of perpendicular sections through the pelvis, are interesting, original, and valuable. Embryology is concisely and clearly given.

In treating of physiological pregnancy and its management, the author recognizes the fact that the thyroid is enlarged during pregnancy, and altered in the great majority of cases. In the diagnosis of pregnancy the cessation of menstruation is considered the strongest presumptive evidence of pregnancy. The author does not mention the Abderhalden test for pregnancy, nor the fact that leukocytosis is usually present, nor does he advise examination under anesthesia in cases where diagnosis is difficult.

In the management of normal pregnancy stress is laid upon the necessity for a physical examination during the early months, and this we think a wise provision. The author measures the pelvis at the first opportunity; there can be no objection to this, and many arguments in its favor. In healthy women he makes little change in diet. His ration of water during pregnancy is six glasses daily. He does not mention the nitrogen partition of the urine if albumin or other abnormalities are found, and relies upon the usual examination, including that for acetone and diacetic acid.

Multiple pregnancy is placed with normal pregnancy, and while superfecundation is recognized, doubt is expressed concerning the existence of superfetation.

The author believes that the placenta becomes detached largely through contraction and shrinkage of the placental site, and that thus becoming a foreign body in the uterus, it stimulates the womb to expel it.

In the section upon the mechanism of labor, there are clear and useful illustrations giving a lateral view of the bony pelvis, and also the iliacus and psoas muscles. From the study of a specimen from which an illustration is given, the author believes that the lower uterine segment is derived both from the body of the womb and from the cervix. A good diagrammatic illustration of the pelvic canal showing its various portions with relation to their situation in or out of the pelvis, naturally attracts attention.

He states that the predominance of LOA over ROP is found in the shape of the fetal ovoid which fits its abdominal concavity into the convexity of the mother's vertebral column. The author states that at the Sloane Hospital the anterior fetal shoulder is always born first as the posterior shoulder is held back in the vagina with the right hand of the obstetrician, while the head is forced gently downward toward the mother's perineum with the left hand, thus causing the birth of the anterior shoulder first. This is done to prevent the posterior shoulder from tearing the perineum. Patients are delivered in the dorsal position. In our experience the lateral position for spontaneous labor is much the best.

The author describes fully and in a most interesting way the management of normal labor, and rightly believes that two vaginal examinations are usually needed, one so soon as the obstetrician arrives, and the other when the membranes rupture. The use of gloves, especially by practitioners who must treat all sorts of cases, is emphasized.

We are surprised to find that ether during labor was so unsatisfactory to physicians and nurses at the Sloane Hospital that chloroform is used. In our experience normal labors can be managed with great satisfaction to all concerned by the careful use of ether. The author's opinion of scopolamin-narcophin anesthesia is not enthusiastic. The author will give anesthesia by nitrous oxide and oxygen a further trial judging from his experience up to the present time.

In preventing ophthalmia the author uses 20 per cent. argyrol solution and repeats the instillation on the third day after birth. Our experience coincides with his that argyrol is practically efficient, and far less irritating than silver nitrate. The author would not repair a torn cervix immediately unless hemorrhage occurred, nor does he mention the repair of the anterior segment of the pelvic floor. Here the experience of the reviewer differs from that of the author. In the immediate repair of considerable cervical lacerations the reviewer has had good union in 80 per cent., partial union in 10 per cent., and no union in 10 per cent. without infection. Lacerations of the anterior segment in our observation are not infrequent. They often cause small but obstinate hemorrhage, and may further produce prolapse and displacement of the urethra. Their immediate repair with catgut has been in our hands entirely satisfactory.

In treating of the care of the infant where birth conditions are abnormal, the author employs a method in alternation with Sylvester's method with the child in the warm tub, which consists essentially in rapidly changing the position of the child. The reviewer has had best results in these cases by unfolding and folding the child with the head downward, keeping the mouth and nose as free from mucus as possible.

In the management of the puerperal period, the author has found codeine a good remedy for after-pains, and his experience coincides with that of the reviewer. He wisely urges against the use of the catheter for the mother during the puerperal period because of the danger of cystitis. The author gives some valuable practical points concerning the best method of dealing in general with patients. He fixes a month after confinement as the usual limit for the attendance of the obstetrician, when the obstetrician should refer the case to a general practitioner.

In treating of lactation the author calls attention to the use of the thermometer in determining whether or not the infant obtains sufficient nourishment. What he describes as inanition fever is a valuable means of diagnosis. The author includes artificial feeding in his practice as an obstetrician, and has devised a Sloane Maternity Milk Set for the modification of milk.

He calls attention to the importance of circumcision in both male and female children, and the experience of the reviewer coincides with his.

The toxemia of pregnancy is clearly and competently treated, the author finding sodium bicarbonate a remedy of the greatest value for pernicious nausea. He describes and illustrates an apparatus for irrigating the colon in cases of acute and threatened toxemia. He uses the hot, wet pack, and has largely abandoned venesection for veratrum viride, nitroglycerine and chloral, he thinks, with better results. He emphasizes with italics the principle that in all methods of treatment it is essential to avoid anything which will either reduce the resistance of the patient or seriously damage any of her organs. The author is a faithful user of the dilating bags, and would soften the cervix in threatened eclampsia by the pressure of the bag. The author, in the treatment of toxemia, has not seen the benefit from the free use of salt solution which many others have noticed with such satisfaction.

In treating of the complications of pregnancy, the author would interrupt pregnancy when complicated in the early months by acute tuberculosis; in the later stages of tuberculous infection there is some difference of opinion.

The author would operate upon patients seized with appendicitis during the early half of pregnancy, but in the latter half, if the inflammation seems catarrhal, he would treat it by rest and ice-bags. While the temperature and blood count may be of value, we do not know a certain method of diagnosis between catarrhal and suppurative appendicitis, and in our experience operation is indicated when pregnancy is complicated by appendicitis.

In the section treating of abortion, some excellent illustrations add to the value of the article. In the treatment of inevitable abortion the author would empty the uterus under anesthesia by the gloved finger unless the case proceeded promptly. In incomplete abortion the uterus should be emptied with the least injury and with the greatest cleanliness, for this purpose a blunt, firm curette, and a sponge-holder are, in the author's experience, essential. He would palpate the uterine cavity to be sure that nothing is overlooked. He illustrates a glove finger dilator which seems to the reviewer much inferior to the solid Hagar dilators, or to that of Newell.

The author devotes one section to hemorrhage, antepartum, intrapartum, and postpartum. In placenta previa the use of elastic bags is a routine treatment at the Sloane Hospital. The mortality in uncomplicated placenta previa for the mother was 4 per cent., and a maternal mortality of 8.1 per cent. occurred in complicated placenta previa. In complete placenta previa by the use of the bags, the maternal mortality was 14.4 per cent. The infant mortality was 51 per cent. When from these are subtracted those infants premature, the fetal mortality remains 36.9 per cent.

The author calls attention to the fact that when a diagnosis of placenta previa is distinctly made there is in private practice only one safe rule of treatment, namely, to empty the uterus. He emphasizes the statement that it is not always necessary to perform version in placenta previa, and he recognizes the fact that there is a tendency of late to employ abdominal Cæsarean section for primigravidæ with long and rigid cervices where a glove-stretcher dilator must be used in order to introduce a bag. The reviewer's experience with Cesarean section in placenta previa leads him to believe that in well appointed hospitals it is far superior to the glove stretcher dilator, the introduction of bags, or any other method of delivery. We are surprised to find the author advising that in placenta previa the foot should be seized, and that the obstetrician should proceed at once to extraction. This is the most dangerous thing which can be done under the circumstances. When the version has been performed and hemorrhage stopped by bringing down the foot and breech, nothing more should be done in the way of active interference for a time.

In treating of premature separation of the normally implanted placenta, the author, we think, wisely considers toxemia as the main cause. In the treatment of accidental separation of the placenta the author is still wedded to the dilating bag in the cervix, although many prefer to deal with these cases by immediate section.

It is a curious arrangement of the book to find postpartum hemorrhage under the complications of pregnancy, but this, it is stated, arises from convenience in description so that the subject of hemorrhage may be presented as a whole.

In treating of the management of the third stage of spontaneous labor, it is stated that at the Sloane Hospital, twenty minutes are allowed for the separation for the placenta. No better precaution can be taken against postpartum bleeding. The author recognizes the value of packing the uterus with gauze to control or prevent hemorrhage, and in an emergency where gauze could not be obtained, he would use any sterile material available.

In the management of pyelitis complicating pregnancy the author has resorted to nephrectomy, but apparently not to drainage of the kidney. In our experience nephrotomy for drainage has been successful without the interruption of pregnancy.

Justo-major pelves are not classified as deformed pelves at the Sloane Hospital, but justo-minor are, although they are no more deformed than are justo-major. Provided a pelvis is symmetrical, it is not deformed whether it be larger or smaller than the average.

Pelvic contractions and abnormalities are fully dealt with, as are the malformations of the fetus. Dystocia from abnormal presentations receives adequate attention.

In preventing laceration of the perineum, while it is said that the advance of the presenting part must be controlled, anesthesia is not mentioned as a most valuable means of preventing laceration. Illustrations for the secondary repair of the perineum are used to illustrate the primary operation, and there is no reference to the repair of the anterior segment of the pelvic floor.

In the induction of premature labor the author prefers the bag to the bougies because the bougies may cause rupture of the membranes. Among the indications for the induction of premature labor we are surprised to find complete placenta previa and complete separation of a normally situated placenta. In our experience these conditions are so grave that they demand more prompt relief than that afforded by the induction of labor.

There is no more important subject for consideration by the profession and by obstetricians than the use of the obstetric forceps, and we naturally read what the author has to say upon this subject with the greatest interest. In the contra-indications for the forceps he does not mention lack of engagement of the fetal head nor does he lay strong emphasis upon the necessity for engagement and molding for a safe forceps operation. He advises and practises the high forceps operation where the instrument is applied to the head which he says may be floating or may be engaged, and among forceps deliveries at the Sloane Hospital, 1.09 per cent. were high operations where the head might have been floating or might have engaged. The author lays stress upon the need for an accurate diagnosis of the presentation and position of the child, and the relative size of the pelvis before attempting the introduction of the forceps, but the question of engagement and molding does not seem of primary importance in his mind. He uses the solid bladed forceps without axis-traction device, employing Pajot's maneuver when necessary.

The maternal mortality of forceps operations is stated at 1.2 per cent., but death is ascribed to conditions other than the application of the forceps. The fetal mortality in forceps operations of all types was 14.5 per cent., but in the high forceps operations where the head was floating or might have engaged, the stillbirths were 26.2 per cent.

We believe that two statements or misstatements, one among the laity, and one among the profession, have done more than anything else to impede progress in obstetric art. In the minds of the laity the half truth that labor is a natural process, and therfore requires no skilled supervision, has cost the lives of many mothers and children. In the general profession the statement that the obstetric forceps can be safely applied to the fetal head, unengaged and without molding, or floating at the pelvic brim, causes many obstetric tragedies. In direct contrast with the author's fetal mortality in the high forceps operations upon the floating or possibly engaged head, of 26.2 per cent., stands his statement that in his experience Cesarean section is the safest method for securing the birth of a living child.

Symphyseotomy and pubiotomy and vaginal Cesarean section are well described and clearly illustrated, and the author is justly not enthusiastic over vaginal section. He believes that a quick Cesarean section is greatly to be desired, largely because until the uterus is closed the patient is losing blood from its sinuses. The author's results in Cesarean section would, we believe, justify him in extending this method of treatment to placenta previa and cases where the fetal head did not engage during labor.

In dealing with puerperal infection he has faith to believe that as a rule the vagina is sterile within, while the vulva is non-sterile without. He does not bring up the questions of hemolytic bacteria and their importance. His recommendations in the practice of asepsis and antisepsis are standard and excellent, and his conservative treatment of puerperal infection will receive hearty endorsement from the majority of obstetricians. He does not recommend sera because they have failed to produce positive results, but there is hope that vaccines may be of value in infection by the staphylococcus, gonococcus and in colon bacillus infection of the kidneys. He is wisely conservative in the matter of surgical operation in puerperal septic infection.

A tabulated statement regarding infant mortality closes the volume.

The author has fulfilled his purpose in placing on record the statistics of the fine hospital under his charge. He gives to the obstetric profession the results of years of intelligent and thorough work, accurate observation, balanced judgment, and honest statement. His contribution to obstetric literature is a credit alike to him and to his hospital, and an honor to the medical profession.

E. P. D.

Endemic Diseases of the Southern States. By William H. Deaderick, M.D., Member of the Hot Springs Medical Society, the Arkansas Medical Society, etc., and Loyd Thompson, M.D., Member of the Hot Springs Medical Society, the Arkansas Medical Society, etc., Hot Springs, Arkansas. Pp. 546; 117 illustrations. Philadelphia and London: W. B. Saunders Company, 1916.

Until the publication of this book, none had been written to cover solely the endemic diseases of the South, hence the purpose of the authors to supply this omission.

They make no pretention of treating of tropical diseases in general, but simply limit the work to an intensive study of the endemic diseases of the Southland.

The book is divided into six parts as follows: malaria, blackwater fever, pellagra, amebic dysentery, hookworm disease, and other intestinal parasites.

Eight chapters are devoted to malaria, the first dealing with an interesting historical and geographical discussion, following which the etiology is presented in detail, much space being allotted to the mosquito and the malarial organism, and the whole being freely interspersed with plates, tables, and illustrations.

The pathology and clinical history of acute, chronic, and pernicious malaria are well presented, while the chapter on prophylaxis is especially good, being rendered more attractive by many photographic illustrations. The chapter on treatment is of value, combining as it does the views of many writers together with those of the authors, the latter evidently having enjoyed an unusually wide experience in the treatment of this disease.

Blackwater fever is given in much the same intensive manner as malaria. The description is replete with references to the literature, the theories of hemoglobinuric fever being dealt with in detail, the authors themselves conforming to the view more generally accepted today that malaria is essentially and solely the predisposing cause. One omission should be noted in Chapter XI, which deals with the pathology of this disease. In this chapter no mention is made of the condition of the bone marrow in which practically constant and striking changes occur. The chapter on treatment contains the views of various exponents of quinin with a clear-cut expression on the part of the authors as to their opinion.

The sections on the two diseases above discussed compose over half the book.

Pellagra is the next disease, and here again the same thorough study has been made, and, aside from many references, the reports of the Thompson-McFadden Pellagra Commission have been resorted to freely. Not a little attention is given to the various theories advanced as to the etiology, recent researches being discussed in this light.

Amebic dysentery and hook-worm disease compose the next two sections, and require no further comment than to say that they conform in character and length to the descriptions usually found in a system of medicine.

Other intestinal parasites, the last section, offers a brief text-book-like description of the parasites commonly encountered in the South. At the end of the book there is a long bibliography. The book is well bound, and the paper and print are good.

Its special sphere of usefulness will be among the Southern practitioners, though, in view of the frequency with which these diseases may be encountered throughout the United States, its sphere should by no means be limited. A. H. H.

Diseases of the Skin. By Henry H. Hazen, M.D., Professor of Dermatology in the Medical Department of Georgetown University; Professor of Dermatology in the Medical Department of Howard University; sometime Assistant in Dermatology in the Johns Hopkins University; Member of the American Dermatological Association. Pp. 539; 233 illustrations; 4 colored plates. St. Louis: C. V. Mosby Company.

Hazen is to be commended for the excellence of his new book, which is an addition to our dermatological field. The text is written in an entertaining and lucid manner. As the author mentions in his preface, he has omitted several of the rarer conditions, his object having been to write a book for the student and the general practitioner. Photomicrographs of the common eruptions have been added to the clinical pictures, which impresses the reader with the pathological aspects of the various diseases. This addition is to be commended. Hazen has attempted a brand-new classifications of the diseases of the skin, which is very different from that employed in the average text-book. This new grouping of dermatological eruptions might prove at least unusual to conservative writers upon these subjects, but classification is indeed our Waterloo.

The preliminary sections of the book, on diagnosis and treatment particularly, are of distinct value. The pictures are mostly good, but some of the photomicrographs should be omitted from a future edition because of lack of clearness and detail. The few references which are given have been carefully picked and should prove a help for further investigations by the reader. All of the various modern methods of treatment and diagnosis are included in the volume. Typographical errors are comparatively few, and the book is well printed in good clear type and on fine glazed paper, the latter helping tremendously in bringing out the detail of most of the photographs. The volume shows the work the author has put into his subject, and is to be recommended to the medical public.

F. C. K.

PERORAL ENDOSCOPY AND LARYNGEAL SURGERY. By CHEVALIER JACKSON, M.D., Professor of Laryngology, University of Pittsburg, etc. Pp. 725; 5 colored plates and 490 illustrations. St. Louis, Mo.: The Laryngoscope Company.

DR. CHEVALIER JACKSON needs no introduction to the medical profession anywhere in the world. His latest book is likewise beyond praise. Most readers will remember the excellence of his first work on *Tracheobronchoscopy*, which was the first published on that subject. The one at present being reviewed is the largest, most complete, and up to date in existence. It is in reality a continuation of his early work, and in some ways supplementary to it, although it is not necessary to have the other for a complete understanding of the subject. In a number of instances, however, the positions taken earlier in the study of the subject have been reversed and numerous modifications in procedure have been introduced. What lends most interest and authority to the work is the recital of the author's methods, derived from his enormous experience, in dealing with different mechanical problems, notably in the removal of foreign bodies; but attention is repeatedly called to the fact that after all this is only one of many uses for endoscopy. While the author still adheres, in the main, to the earlier forms of apparatus used successfully by him, he gives credit both in text and illustration to the instrumental devices and technic of other operators and says that that form of instrument is the best which the individual operator finds easiest to use. His position in regard to anesthetics is extreme. He uses no anesthesia for children under seven, none for esophagoscopy at any age, except very occasionally for large foreign bodies, and but little or none for laryngoscopy, except for removing specimens or neoplasms. For tracheobronchoscopy, local anesthesia is usually needed only for the removal of foreign bodies in adults. General anesthesia he rarely uses. While this seems to be satisfactory in Jackson's hands, most endoscopists have difficulty in following his rule closely in this respect. The whole book, telling as it does of the marvelous success and skill of Dr. Jackson and his methods, is an inspiration for the laryngologist interested in this line of work, and the directions are so simple and accurate, the illustrations so understandable, that it is a liberal education for the young endoscopist. A notable feature of the book is the systematic and consecutive arrangement of subjects and the accurate explanatory illustrations, many of which are original photographs by the author or his own personal drawings. The chapter on Suspension Laryngoscopy has been written for the author by Professor Killian himself, and is a complete exposition of the subject. In addition to the endoscopic portion of the work, there are practically one hundred pages devoted to tracheotomy, dilatation of chronic laryngeal stenosis, laryngostomy, decannulation, and malignant disease, with the technic of thyrotomy and laryngectomy, all most admirably presented. Another unusual feature of the work, and one that will appeal to the profession, is the very complete bibliography attached, consisting of six hundred and forty-seven references. Altogether, the book makes fascinating reading, and is indispensable to anyone who is called upon, even occasionally, to do endoscopy. G. M. C.

Pellagra. By George M. Niles, M.D., Gastro-enterologist to the Georgia Baptist Hospital, Wesley Memorial Hospital, and Atlanta Hospital; Consulting Gastro-enterologist to the Atlanta Antituberculosis Association and to the Moore Memorial Clinic, Atlanta, Georgia. Second edition. Pp. 261; 20 illustrations. Philadelphia and London: W. B. Saunders Company, 1916.

Although a tremendous amount of work and numerous investigations have been made in the study of pellagra, particularly in regard to the etiology of this puzzling disease, in the present edition the author is still compelled to publish theories rather than facts The painstaking studies of the United States Army surgeons and those in marine hospital work, as recorded in the present volume, cannot be too highly commended, although still lacking in absolute proof. Niles has brought the present edition strictly up to date.

The various views of the different authorities are freely given and discussed. These views, however, are so diversified that they no doubt would prove puzzling to the average reader unless rather well versed on the general subject of this affection, and possibly it might have been more lucid if the author had expressed somewhat more definitely his own personal view-point.

Enlarging upon Lombroso's dictum of spoiled corn being the etiological factor in the production of pellagra, it is suggested in this volume that spoiled carbohydrates may also prove causative. Goldberger's recent work is quoted, in which he apparently found that an unbalanced or deficient diet was the cause of the disease. The new edition contains eight more pages than the last and several new illustrations. F. C. K.

A TEXT-BOOK OF THE PRACTICE OF MEDICINE. By JAMES L. ANDERS, M.D., PH.D., LL.D., Professor of Medicine and Clinical Medicine, Medico-Chirurgical College, Philadelphia. Twelfth edition. Pp. 1336; illustrated. Philadelphia and London: W. B. Saunders Company.

IT is almost a sufficient review to state that twelve editions of Anders's *Text-book of the Practice of Medicine* have appeared in the past eighteen years. The reasons for its popularity lie chiefly in its clearness and in its completeness. It is at the same time clear and concise and has an index far superior to most works of its kind. Another factor which adds to its value is the giving of references to the literature, and this indeed might be done even more freely.

The present edition has been brought up to date and considerably revised. For the most part the new matter is well presented and worthy of inclusion, but some of the new matter mentioned in the preface receives scant attention in the text; thus the phenolsulphonephthalein test is mentioned in the preface, but does not appear in the index and only incidentally in the text. In fact, the preface details five new sections, and these sections together occupy no more than two printed pages. The title of one of these sections is given in the preface as Vagotomy, an alarming misprint, which will certainly lead some to disappointment. As a whole, the book is excellently edited and published, except for diacritical marks, those bugbears of publishers and printers in this country. One may take one's choice, for example, of Báràny or Barány and of d'Espinés sign or d'Espine's sign.

These, however, are small faults and detract but little from the value of this book which can most strongly be recommended.

O. H. P. P.

Infant Feeding and Allied Topics. By Harry Lowenberg, A.M., M.D., Assistant Professor of Pediatrics, Medico-Chirurgical College of Philadelphia; Pediatrist to the Mt. Sinai Hospital, the Jewish Hospital, and the Jewish Maternity Hospital; Assistant Pediatrist to the Medico-Chirurgical Hospital and the Philadelphia Hospital, etc. Pp. 382; 64 engravings 30 plates, 11 in colors. Philadelphia: F. A. Davis Company, 1916.

In addition to the usual subjects pertaining to breast and bottle feeding, rickets, scurvy, spasmophilia, the "eruptive diathesis" and pyloric obstruction are considered. Dr. John B. Deaver has written the section on the surgical treatment of the latter condition. The book is based almost entirely upon the personal experience of the author. The aim in writing it has been to make it largely clinical and practical, and the presentation of a medley of views of different authorities therefore has been "studiously avoided." This aim has been fulfilled. Few opinions appear except those of the author and the results of the many lines of recent interesting research apparently play a small part in the formulation of his opinions. As a result, there are ample grounds for differing, in many particulars, from the author's views. The student who thoroughly masters the contents of the book will have added to his store of practical knowledge, but not to his grasp of the subject of infant feeding. J. C. G.

The Art of Anesthesia. By Paluel J. Flagg, M.D., Lecturer on Anesthesia, Fordham University Medical School; Anesthetist to Roosevelt Hospital; Instructor in Anesthesia to Bellevue and Allied Hospitals, New York, etc. Pp. 333; 136 illustrations. Philadelphia: J. B. Lippincott Company, 1916.

This book is intended as a groundwork upon which the student, interne, and general practitioner may acquire a more comprehensive knowledge of the art of anesthesia. A brief history of anesthesia and its development is given and a *résumé* of the entire field of anesthesia is given by defining and describing general, local, and mixed anesthesia.

General anesthesia is then taken up in detail, the facts being grouped under the stages induction, maintenance, and recovery. At the conclusion of the elaboration of these stages there is appended a summary, valuable in reviewing, teaching, and quizzing.

All the various methods of administration are described fully and clearly. The indications for and contra-indications are discussed at great length. Local and spinal anesthesia are treated in a somewhat limited manner.

Medication before and after anesthesia is taken up and discussed from the stand-point of psychology, drugs, their time of usefulness, the dose and the administration.

Several pages and many illustrations elaborate upon the various positions that patients must assume on the operating table, and the influence such position may have on the administration of the anesthetic.

The writer lays the emphasis upon anesthetization that it deserves, and warns us that it is an art, and one that needs constant study and attention. He states that the more one administers anesthetics the more careful he should of necessity become. Carelessness and inattention are not to be countenanced.

The work is a good one, comprehensive, well written, well illustrated and up to date. E. L. E.

Gynecology. By William P. Graves, A.B., M.D., F.A.C.S., Professor of Gynecology at Harvard Medical School; Surgeon-in-Chief to the Free Hospital for Women, Brookline; Consulting Physician to the Boston Lying-in Hospital. 303 half-tone and pen drawings and 122 microscopic drawings. Philadelphia and London: W. B. Saunders Company, 1916.

This latest contribution to the already large number of books on gynecology is indeed a master work. Although ostensibly it is merely a single volume text-book, in reality it may be said that it is almost a series of monographs condensed into tangible form, supplemented by the personal experiences of the author. Many other books have been consulted in the preparation of the work and due credit is given throughout whenever reference is made to the work or investigations of another. The author, however, does not blindly follow the statements of preceding authors, as is so often the case in medical literature, but whenever a point is still debatable the arguments are given for and against it, followed by the author's personal views on the subject.

The book is very broad in its scope, including the urinary organs and lower intestinal tract in addition to a most valuable section on the relationship of gynecology to the general organism, in which it is shown how the various diseases of the female generative organs can influence practically every organ and tissue in the body. Such a chapter as this, which is along original lines in text-book composition, will be of inestimable value to the general practitioner, embracing, as it does, the latest views on the ductless glands.

The sections on treatment are well written and contain the most recently accepted methods; the radium treatment of cancer is especially well handled, conservative and guarded statements being made concerning its value. The various gynecological operations are fully described and profusely illustrated, the author having selected the most important operations of each class for discussion. Many of the operations described are original and quite ingenious.

One of the many unusual features of the book is that most of the illustrations have been drawn by the author himself, who, many years ago, was a pupil of the celebrated Broedel.

The work is undoubtedly one of the best of its kind, is fully in compliance with all expectations, and will certainly enjoy great popularity. F. E. K.

INDEX OF PROGNOSIS AND END RESULTS OF TREATMENT. By VARIOUS WRITERS. Edited by A. RENDLE SHORT, M.D., B.S., B.Sc. (Lond.), F.R.C.S. (Eng.). Pp. 570. New York: Wm. Wood & Co.

THIS book is the fruit of the combined efforts of twenty-four contributors, each especially fitted to treat of the subject allotted him. Its nearly 600 finely printed pages afford ample space for a comprehensive study of, that so often briefly dealt with phase of medicine, prognosis. The subjects are dealt with in alphabetical order so that but a moment's search is required to put one's finger on a desired topic.

Of especial interest are the sections on diseases of the heart, arteries and kidneys and that on tuberculosis in all its manifestations. The fact that the writers are not cramped for space has made it possible for them not only to take up separately the individual possibilities in a case, but these in combination and also in association with other diseased conditions. The writers have presented a uniform front in tracing eventualities to their real underlying cause. In this way the book becomes really more than an index of prognosis, for when the dominant factor in the determination of a prognosis is clearly grasped one has at his command the rational basis for treatment.

An instructive phase of the book is the discussion of prognosis from the standpoint of what mode of treatment has been used. The results of different medical and different surgical treatments are compared and when the treatment may be either medical or surgical the results in either case are shown.

What weakness there is in the book it shares with books of a similar nature which seek to be all-inclusive. There is of necessity a great deal of repetition and the splendid way in which big subjects are handled is offset by less comprehensive and careful dealing with minor subjects and the inclusion of information of a trivial nature regarding matters of little interest which have crept into the book, mainly, it would seem, to justify as far as possible the title of index. A. A. H.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Transvesical Prostatectomy under Local Anesthesia.—Perrier (*Jour. d'Urol.*, 1915, vi, 509) says that local anesthesia saves the strength of the patient, diminishes shock and avoids damage to the kidneys by doing away with inhalation anesthesia. He employed the following method in 5 cases: The abdominal and vesical walls were anesthetized by infiltration with a solution of novocain-adrenalin of 1 to 200 strength, the quantity employed varying according to the obesity of the patient. The perineum is also infiltrated with the same solution in a line in front of the anus between the two tuberosities of the ischia. This will permit the deeper injections without pain. The index finger being introduced into the rectum, a long needle (12 to 15 cm.) is employed to make the injections under the capsule of the prostate. One feels, according to the quantity of fluid injected, the capsule rise and become tense, proving that the injection is being made in the proper space. With the same needle the sacral nerves are injected with a solution of 1 to 100, as indicated by Braun. His method is briefly as follows: With the patient in the tailor position, the needle is introduced parallel to the direction of the lower part of the sacrum, searching with it for the border of the sacrum. Then groping along the internal surface of this bone, parallel to the median line, one strikes the bone. Then along this track, *i. e.*, from about the fifth to the second sacral foramen, one injects about 20 cm. of the 1 per cent. novocain-adrenalin solution. Then the needle is withdrawn to the edge of the sacrum and passed in the direction of the innominate bone, parallel with the median line. In this direction the bone will be struck at a depth of 9 to 10 cm. About 20 cm. of the 1 per cent. solution is then injected. Finally, 5 cm. are injected between the coccyx and rectum from the same point. Braun used this method alone for prostatectomies. It paralyzes the anal sphincter, ureters, prostate, and bladder.

Subastragaloid Arthrodesis in Lateral Deformities of Paralytic Feet.—Willard (*Amer. Jour. Orthop. Surg.*, 1916, xiv, 323) presents the following operation, devised by G. G. Davis, about nine years ago, and performed in 8 cases by Willard. Two incisions are made, one on the inner side of the foot, about a finger's breadth below and in front of the internal malleolus, on the level of the sustentaculum tali; the other on the outer side immediately below the external malleolus. Both incisions are parallel to the long axis of the foot, and are about an inch and a half in length. Through the inner incision the posterior tibial tendon can be exposed and drawn aside and the astragalo-scaphoid joint between the astragalus and sustentaculum tali can be reached. With a small curved gouge these joint surfaces, together with the lower surface of the astragalus and the upper surface of the os calcis which lie between them, are roughly dug up. Through the external incision the sheath of the peroneus brevis and tertius can be opened and these tendons drawn aside. The joint between the os calcis and astragalus can now be easily found by pushing the gouge through from the inner incision. The outer portion of the adjoining surfaces of the os calcis and astragalus is thoroughly roughened. The completed operation should give two rough denuded bone surfaces with numerous loose fragments of bone and cartilage lying between them. The upper of the two surfaces is the interior and inferior surfaces of the astragalus; the lower, the posterior surface of the scaphoid and the entire anterior two-thirds of the upper surface of the os calcis. Only the skin wounds are sutured and the foot is fixed in a plaster-of-Paris dressing extending to the knee. Great care must be taken to fix the foot in the proper position (the sole of the foot being at right angles to the line of weight-bearing). Remove the dressing at the end of a week, inspect the wound and replace the foot in plaster in proper position. The patient is allowed to walk in a cast at the end of four weeks and the cast is removed in eight weeks, and, unless the paralysis of the other portions of the leg demand it, no braces are put on. From a study of Willard's and other cases, subastragalar arthrodesis seems to be the operation of choice in the cases of paralytic feet that show lateral deformity, but in which some muscle power still persists, and in which operations tending to interfere with motion at the ankle are not to be desired. There is no tendency to recurrence of the deformity.

Foreign Bodies in the Respiratory Tract.—Green and LeWald (*Ann. Surg.*, 1916, lxiii, 656) say that the most frequent occurrence of foreign bodies in the respiratory tract is in children, 69 per cent. in children up to twelve years of age (Brünings), the greatest frequency being at the age of two years. Some bodies, as a seed or a nut, will hardly be of a sufficient density, to show in a skiagraph. After the *x*-rays and of equal importance, but secondary in sequence from a diagnostic stand-point, comes the direct inspection of the larynx, trachea and bronchi by means of the bronchoscope. Three interesting and successful cases are reported. All recently aspirated foreign bodies should first be sought by the roentgen-rays and the bronchoscope, without delay, and removed if possible through the mouth. Failing to remove them through the mouth a tracheotomy should be done and another attempt made by means of the bronchoscope. Failing in this the tracheal wound should be held widely open by wires or a large tube in the hope that the foreign body may be coughed out. If immediate removal by these methods fail, a period generally elapses in which the patient may undergo secondary changes in the lung, such as pneumonia, gangrene, abscess, and generally an overlying empyema. If the patients recover from these acute infectious processes, they pass into the class of deferred cases with the foreign body still present as an aggravating factor in their chronic lesion. Removal of the foreign body in these deferred cases does not always effect a cure. The lung abscesses must be treated along surgical lines and even then we cannot always hope for a cure, but rather only an amelioration of their affliction.

The Aperiosteal Stump and its Care.—Lyle (*Ann. Surg.*, 1916, lxiii, 674) says that modern surgical technic now demands that all amputations of the lower extremity yield stumps capable of directly supporting the whole weight of the body. The essential points in the technic consist in removing a small cuff of periosteum (0.5 cm. in depth and leaving no shreds of periosteum) from the bone stump and spooning out the marrow cavity for a like distance, plus the after medicomechanical treatment of the stump. The best-formed stump, if not quickly put to use as a real support, may become atrophied and useless. After the operation the patient is put to bed with the leg elevated. As soon as the wound is healed begin to massage the stump twice daily, and after each treatment rub in a 2 per cent. solution of salicylic acid in olive oil. At night bathe in a warm sodium carbonate solution. Protect the stump with lamb's wool. Place a box at the foot of the bed and have the patient press the stump against it from five to ten minutes three times a day; then four times; finally every hour. After each treatment energetically flex and extend the hip and knee. Now begin standing exercises. Rest the stump on a bran bag or a cane-seated chair, at first placing the weight evenly on both legs; later place all the weight on the stump. At the end of two weeks the patient should be able to wear a peg leg, later a permanent prosthetic appliance which directly receives the weight through the end of the stump. No stump should be considered good unless it is capable of supporting the whole weight of the body. Insist that the permanent artificial leg be built on the end-bearing principle.

High Intestinal Stasis.—Sweet, Peet and Hendrix (*Ann. Surg.*, 1916, lxiii, 720) working on the lower animals on the problem of the cause of death in either the mechanical or functional, *i. e.*, paralytic, obstructions of the upper bowel, report two findings of surgical interest. First, is the added demonstration of the fact that a gastro-enterostomy opening does not function in the presence of a normal pylorus. The second offers the explanation of the similarity between acute pancreatitis and acute high obstruction; they are alike because they are both essentially the same thing, an intoxication with the toxic products of protein cleavage, in pancreatitis certainly due to the proteolytic ferment of the pancreas, in high obstruction not necessarily, perhaps, but in the writers' opinion in all probability, the same toxin, produced by the same ferment. In pancreatitis the escape of the products of the digestion of the pancreas into the tissues permits the intoxication; in obstruction the conditions of obstruction permit the absorption of toxic products, which under normal conditions would either not be formed, or if formed would be immediately broken down into non-toxic products.

Postoperative Ileus.—Thompson (*Surg., Gynec. and Obst.*, 1916, xxii, 688) says that during the fall and winter of 1914 and 1915 he had operated on 4 cases of obstruction by short-circuiting methods and drainage. Enterostomy was done, and later ileo-ileal anastomosis. The result, recovery. After a series of experiments on dogs he settled upon the following technic for short-circuiting: Make an incision in the abdomen for the short-circuiting above and to the side of the laparotomy incision. Handle the intestine gently and as little as possible. Keep away from the obstructing adhesions. Ileus is caused by the breaking up of adhesions in the presence of pus. Avoid pulling on the mesentery. Make a lateral anastomosis, if possible, between healthy ileum above and ileum just proximal to the ileocecal valve, as this portion is seldom involved in ileus. Do an appendicostomy or cecostomy to allow for drainage and for the introduction of fluids into the system. Thompson believes that the best results are obtained in the treatment of inflammatory ileus by enterostomy and drainage in cases that are so ill that radical measures would be fatal. Enterostomy should be done rapidly and without disturbing the adhesions. When the patient recovers ileo-ileal anastomotic closure of the enterostomy wound and cecostomy or appendicostomy will complete the cure. In favorable cases ileo-ileal anastomosis with cecostomy or appendicostomy for drainage and to relieve the back pressure in the colon, gives the best results. By short-circuiting and putting the damaged gut at rest it may be restored to health and function even after vascular changes have taken place. The mortality of resection for this disease is too high to give it a place in the treatment of inflammatory ileus. The adhesions should not be broken up or the damaged gut handled in the operation.

Some Experiments with Rubber Gloves.—Black (*Surg., Gynec. and Obst.*, 1916, xxii, 701) gives the results of experiments with the blind who do all their reading with the fingers, to show the effects of the rubber gloves on the tactile sense. The use of medium-weight rubber gloves requires the blind to use an average of twenty-two seconds more in reading one hundred words of Braille than with the bare fingers, namely, forty-eight seconds with the bare fingers, and seventy seconds with medium-weight gloves. Or, in other words, there is a loss of nearly 50 per cent. in the sense of touch judging from the results of this experiment. The tactile sense is materially improved by putting on wet instead of dry gloves, the difference being an average of five seconds or a little less than 10 per cent. Gloves put on with oil on the hands give a slight improvement over dry gloves, namely, sixty-eight seconds as against seventy seconds. The tactile sense diminishes in direct proportion to the thickness of the gloves as shown in the first series of observations where thin gloves showed an average of seventy-one seconds, thick gloves showed an average of one hundred and six seconds as against an average of forty-eight seconds with the bare fingers. A marked improvement in the tactile sense is brought about by the use of carefully fitted gloves as shown in the second series where, by care in fitting, the average was reduced from seventy to sixty-six seconds. Gloves put on wet give the most favorable opportunity for exercising the sense of touch and gloves put on dry the least favorable.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

On the Toxicity of Various Commercial Preparations of Emetin Hydrochlorid.—Levy and Rowntree (*Arch. Int. Med.*, 1916, xvii, 420) introduce their article by stating that in view of the widespread use of emetin hydrochlorid for the treatment of amebic dysentery and of pyorrhea alveolaris, more precise knowledge of the toxicity of the commercial preparations employed is highly desirable. They describe two cases of poisoning with a fatal result in one of these cases. The fatal result occurred in a man who received, daily, subcutaneous injections of emetin hydrochlorid over a period of twenty days for the treatment of amebic dysentery. The average daily dose was 1.5 grains; the total amount he received was 29 grains. A previously existing diarrhea was at first apparently somewhat ameliorated then markedly intensified. The diarrhea stopped five days after withholding the emetin. On the sixteenth day of treatment the patient complained of nausea and abdominal pain and signs of acute renal insufficiency began to develop. The evidences of kidney involvement increased rapidly, with blood in the urine and diminution in the phenolphthalein output along with an increase in the non-protein nitrogen of the blood. The patient finally developed bronchopneumonia and died with symptoms of vasomotor collapse. The other patient who developed toxic symptoms was an undernourished woman who received four subcutaneous injections of 0.5 grain of the drug at daily intervals for the treatment of pyorrhea alveolaris. An intense diarrhea developed, associated with abdominal pain and tenesmus, which ceased six days after discontinuing the emetin treatment. At the same time she was in a toxic delirious state, which lasted for one week. These symptoms were quite out of proportion to the moderate dosage employed, and the particular preparation was suspected of being unusually toxic. This suspicion was apparently confirmed by the severe toxic symptoms with fatal result that followed the injection of corresponding doses of this same preparation in animals. The authors then proceeded to investigate the toxicity of five commercial preparations of emetin hydrochlorid, in the course of which investigation sixty-two animals were used. They found that the toxic symptoms vary considerably but the principal toxic effects observed were vomiting, diarrhea, marked albuminuria, muscular weakness, development of cardiac irregularity. The authors also cite a number of reported cases of poisoning in which the chief clinical manifestations were marked diarrhea, and peripheral neuritis. The case reported by them is the first fatal case so far in the literature. It is also important to note that toxic symptoms may develop after the administration of emetin has been discontinued. Since the most frequent toxic symptom is diarrhea, it is necessary to warn against further emetin treatment upon the recurrence of dysenteric symptoms in every case of amebic dysentery. The authors offer the following suggestions with regard to a rational emetin therapy. Individualization by close clinical observation is essential both for the success and safety of the treatment. Patients may differ markedly in their susceptibility to the drug, and the various commercial preparations vary widely in toxicity. The treatment should be given in courses, at intervals of several days or a week. The subcutaneous route is the one of choice. Individual dosage and the duration of each course must be determined by the exigencies of the case. One-third grain three times a day for a week or ten days is usually a safe dosage in amebic infections. It is rarely necessary to give more than 1.5 grains daily. In the treatment of pyorrhea, Bass and Johns advocate 0.5 grain daily for from three to six days, and maintain that no case need have more than six days' treatment. Under ordinary circumstances this seems well within the margin of safety. It must be borne in mind, however, that the administration of even relatively small doses over a long period of time may prove harmful. The large dosage advocated by Baermann and Heinemann is unnecessary and dangerous. Intravenous injections should be employed only in extreme cases. If this mode of administration seems imperative, small doses well diluted (0.5 grain in 100 c.c. salt solution) should be slowly given, and the blood-pressure should be carefully observed during the injection.

Diarsenol versus Salvarsan.—GARDNER (*Jour. Am. Med. Assn.*, 1916, lxvi, 1303) writes concerning diarsinol which is a substitute for salvarsan manufactured in Canada. The literature on this new preparation is meager, but apparently it differs only slightly from salvarsan. Gardner has given over 300 doses of diarsenol, employing the same technic as in the case of salvarsan. Only three patients have experienced any reaction. He gives it intravenously by the syringe method in concentrated solution. The average patient receives from ten to fifteen doses, depending on the stage of the disease and on the strength of the Wassermann reaction. These doses are given every other day, beginning with a half-dose and increasing the dosage so that the third is a full one of 0.6 gm. By this method, the author believes that he has obtained much better results than by giving the remedy at intervals of one week, two weeks or a month. Gardner believes that the clinical results and the diminution in the positive Wassermann in patients treated with diarsenol compare very favorably with the results obtained by salvarsan therapy. He found that both salvarsan and diarsenol are more liable to be followed by nausea and shock than neosalvarsan.

In the administration of diarsenol the author noted that some solutions remained a light color while others became dark almost immediately. He attributes the change in color to oxidation of the solution and the solutions which oxidized rapidly seemed to be those which usually caused the reactions.

Emetin in the Treatment of Amebic Abscess of the Liver.—DOPTER (*Paris Médicale*, 1916, vi, 243) again calls attention to the beneficial effects of emetin in treating amebic abscess of the liver. His experience now consists of twelve cases and while he is convinced that emetin is of great value in its effect in destroying amebæ, he does not advocate the emetin method alone for the treatment of amebic abscess of the liver but urges its combination with the proper surgical procedures.

The Spleen.—MAYO (*Jour. Am. Med. Assn.*, 1916, lxvi, 716) reviews briefly the present status regarding the knowledge of the functions of the spleen. He speaks especially of the effects of splenectomy in diseases for which this operation has been recommended during the past few years. Patients with anemias associated with enlargements of the spleen are cured or greatly benefited by splenectomy. The syndrome called splenic anemia, the terminal stage of which is known as Banti's disease, may be cured by removal of the spleen in a high percentage of cases. In the later stages, after ascites has developed, and the liver has become cirrhosed, but little may be expected from the removal of the spleen and yet Mayo has seen several patients in this terminal condition cured by splenectomy. Splenic anemia with adult characteristics is not infrequently seen in childhood, and is promptly relieved by splenectomy. Mayo says it is quite probable that the pseudoleukemic anemia of von Jaksch is merely the infantile type of splenic anemia, the increased leukocytes being merely a difference in the reaction of the blood due to infancy. With the splenic anemias may be classified Goucher's disease. His experience in three cases of this disease has shown that in the earlier stages the condition is cured by splenectomy. One of the most interesting anemias of splenic origin is the so-called hemolytic jaundice, a disease of the young, accompanied by acholuric jaundice, that is, there is no evidence of biliary obstruction, bile is present in the stools and there is no itching. There are two types of this disease, one the familiar type of Minkowski which often affects several members of the same family and is less severe in its manifestations, many patients living out a life expectancy. The other is the acquired type of Hayem and Widal which comes on during puberty or adolescence and usually ends in death. In hemolytic jaundice the patient suffers from crises accompanied by tenderness over the liver and spleen, an increase of temperature and quickness of pulse. Based on an experience of nine splenectomies for hemolytic jaundice the author states that no other operation gives more brilliant and striking results. Within twenty-four hours the jaundice begins to disappear, and in a few days the patients perhaps for the first time have clear complexions; the anemia is rapidly overcome and they remain well. Eppinger first called attention to the remarkable improvement of the patient after removal of the spleen in pernicious anemia. Although sufficient time has not elapsed to say that these patients are permanently cured no other means of therapy has so promptly brought about an improvement in the condition of the patient, and so definitely relieved the anemia. It is true that in the late stages when there are spinal cord changes these changes do not disappear, although the condition is marvelously improved, nor do all the characteristic cells of pernicious anemia disappear from the blood. Judging from the effects observed in nineteen patients Mayo feels justified in performing splenectomy in selected cases of pernicious anemia, and has at least the hope that if it is done sufficiently early in the course of the disease, it will permanently check if not cure the condition.

The Springs at Saratoga: Their Value in the Treatment of Disease.—Thompson (*Med. Record*, 1916, lxxxix, 589) calls attention to the great therapeutic possibilities of the springs at Saratoga comparing them with well-known spas in Europe. Now that the springs have come into state control much is to be hoped for in increasing their therapeutic possibilities, for it is indeed the method of state and municipal control which has placed the principal European spas upon their high plane of efficiency. So far as chemical composition of the waters is concerned the springs at Saratoga are similar and often superior to corresponding European Springs. The many different springs of Saratoga which may be drunk fall naturally into three general groups, in each of which a half dozen or more of the most active and copious springs are included. These are: (1) the saline laxative group typified by the long-familiar Hathorn and Congress waters; (2) the alkaline saline group, typified by the geyser spring, in the waters of which alkalinity is the essential feature, together with medicinal quantities of iron and lithium, and (3) the alkaline, iron or chalybeate springs, typified by the karista, which yields a strong excess of ferrous carbonate. All of these waters are copiously charged with natural carbonic acid gas, which renders them more palatable and efficient, and in such of them as are used for bathing, excites distinct cutaneous reaction. With the exception of sulphur the waters at Saratoga contain all of the important mineral or inorganic chemical ingredients of the body, and their drinking affords opportunity for the replacement of these ingredients, as well as for added solvent, diuretic and evacuant effects. The saline laxative or aperient waters of the Congress and Hathorn No. 1 springs are those upon which the more than national reputation of Saratoga Springs was first built. Their laxative effect is due to a high percentage of bicarbonate of magnesia, together with sodium sulphate and other salts. They are useful in cases of chronic constipation, hepatic congestion, cirrhosis, chronic arthritis, arteriosclerosis with high tension, obesity, gout, diabetes, and similar disorders of metabolism. The second group are antacid and are beneficial in gastric hyperacidity, rheumatism, gout, lithemia, gravel, neuritis, etc. These waters resemble French vichy closely. The third group are valuable in cases of chronic anemia and retarded convalescence. Thompson says in comparing the Saratoga waters with those of foreign spas, no claim can be made for them as a "cure-all," but it is proved that the number and variety of the springs is exceptional, that the supply of waters for both drinking and bathing is now abundant, the climate and surroundings are in every way attractive and the resort is most accessible. They should be tried by invalids who have heretofore visited foreign spas and in properly selected cases results may ultimately be obtained fully comparable to those of the most successful foreign resorts.

The Results from Blood Transfusion in the Treatment of Severe Posthemorrhagic Anemia and the Hemorrhagic Diseases.—PETERSON (*Jour. Am. Med. Assn.*, 1916, lxvi, 1291) says that the transfusion of blood, intramuscular injections of whole blood, and intravenous and subcutaneous injections of homologous serum are the most efficient measures, and are of value in the order named in the treatment of hemorrhage and the hemorrhagic diseases. In severe cases of acute posthemorrhagic anemia, blood transfusion is the best, and at times the only efficient means to save life. In chronic posthemorrhagic anemia, provided the cause of the bleeding is removed or remedied, no other means will compare in efficacy with transfusion of blood to stimulate the blood-forming organs. Transfusion of blood has on numerous occasions proved effective in pathological hemorrhages after the failure of all other measures. In some cases, when the blood of one donor has proved ineffectual, the use of blood from another donor has brought about striking results. From a practical point of view, the best clinical results have been obtained in hemorrhagic disease, when a young healthy donor, not fully matured, could be secured. Since there is no method of standardizing blood as a therapeutic agent, variable results must be expected. When properly safeguarded by preliminary tests, the procedure is attended with a majority of favorable results and comparatively few failures.

Vaccine Treatment.—HEKTOEN (*Jour. Am. Med. Assn.*, 1916, lxvi, 1591), in the summary of his article, states that it may be concluded that the general results so far from the routine use of commercial vaccines, polyvalent and mixed, have no value as evidence for or against the curative usefulness of vaccine treatment, and hence no value, either with respect to the soundness of the theory on which vaccine treatment primarily has been developed. In subacute and chronic localized infections, the results appear to indicate that specific vaccines properly and skilfully used have value, quite likely because they increase the production of specific antidobies, as demanded by the theory, but probably also because they stimulate leukocytic and other activities. In typhoid fever and possibly also in other infectious diseases, the intravenous injection of specific vaccines and also of other substances may induce crisis and prompt recovery. The mechanism of this action is not fully understood; but as it involves something more than or different from specific stimulation of the production of antibodies, it cannot be interpreted in terms of the current conception of the action of vaccines.

The Excretion of Salvarsan after Intravenous Injections of Concentrated Solutions.—STERN—*Deutsch. med. Wchnschr.*, 1916, xlii, 416) has determined from his observations in a large number of cases that the excretion of salvarsan following the injection of the drug in concentrated solution is much slower than when it is given in large quantities of a more dilute solution. This fact makes him conclude that the injection of concentrated solutions of salvarsan is of greater therapeutic effect because of the presence of the remedy in the blood and body fluids for a longer period of time. The use of concentrated solutions for intravenous injection is far more practical because of the greater simplicity of technic of administration, less apparatus required for the injections and no assistant necessary, etc. The method of giving salvarsan in concentrated solution is especially applicable to the newer modifications of salvarsan—neosalvarsan and sodium salvarsan.

The Vitamine Solution of the Pellagra Problem.—Wood (*Jour. Am. Med. Assn.*, 1916, lxvi, 1447) says that there is no doubt in the minds of a large number of the students of pellagra that the deficiency theory of Goldberger is correct. Wood says that up to recent years in the South especially, corn was simply crushed between two stones and the only thing removed was the coarse particles of outer skin or husk. This method of milling has largely been replaced by steam or electric milling. By this process the corn is subjected to heat in order to loosen the outer coarse husk. This element, the degree of heat used, may be an important factor in destroying vitamines since they are killed at 120° C. After the heating process the grain is passed into a "degerminator" which removes the germ. This is done because the germ contains such a large amount of fat that rancidity would soon occur if it were left in the meal. Besides this the germ would give to the meal a yellow color which by modern standards is considered undesirable. The offal, which contains the germ, husks, and bran, some flour and flinty portion of the grain, constitutes about 30 per cent. of the entire weight of the grain. This is known as "corn chops" and is fed to cattle. The remaining endosperm is finely ground and the product is known as granulated cornmeal. Wood believes not only that pellagra is a deficiency disease but that the deficiency can be definitely attributed to the modern method of corn milling. Deterioration of corn may also be productive of pellagra because the germ is the portion of the grain most subject to the action of molds and animal parasites. Wood has noted that pellagra is practically unknown in sections of the South where, because of inaccessibility to railroads, the inhabitants still use the old-fashioned ground whole meal.

The Influence of Salicylates on Metabolism in Man.—Denis and Means (*Jour. of Pharm. and Exper. Therap.*, 1916, viii, 213) report results which show in the case of two normal men that the administration of large doses of sodium salicylate (up to 6.6 grams per day) produces an increase in the excretion of nitrogen, phosphates, and uric acid. In one case, this increased nitrogenous metabolism was accompanied by an increase in the basal metabolism and symptoms of salicylate intoxication. In the other case and in one mildly septic case, a much greater increase in the urinary excretion of nitrogen which extended throughout the after period was observed but there was no increase in the basal metabolism and no symptoms of intoxication occurred. No change in the respiratory quotient occurred in any of these subjects.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Education, Licensing, and Supervision of the Midwife.—Edgar (*Amer. Jour. Obst.*, March, 1916), at the Sixth Annual Meeting of the American Association for the Study and Prevention of Infant Mortality, Philadelphia, November 10, 1915, contributed the opening paper in a discussion upon this subject. He drew attention to the fact that little of a practicable nature has so far been accomplished by this country. There are in the profession, three opinions: (1) The midwife must be abolished. (2) The midwife should be ignored and left to her own devices. (3) The midwife should be raised to a higher plane by proper education and State control. Based upon a large experience, Edgar states that the first proposition, in his judgment, is impossible until there is some better substitute for the midwife. The second, namely, that the midwife be ignored and left to her own devices, he thinks unworthy of consideration; the third is, at present, the only practical way of dealing with the problem. At present, physicians and trained nurses are required to receive special instruction in practical obstetrics before they are permitted to enter upon practice. Although about 40 per cent. of the confinements in this country are cared for by midwives, these persons are, except in rare instances, ignorant, untrained, incompetent women, whose bad practice cause death and blindness in infants, and suffering, ill health, and death to mothers. At present, we cannot eliminate the midwife, and whether we shall ever be able to do so remains an open question. If the midwife cannot be eliminated, cannot she be so trained, and her action so regulated, that she will cease to be a danger to the community? It may be interesting to know what is the greatest source of puerperal mortality and morbidity. In the past, many practitioners of medicine were undoubtedly more dangerous to their parturient patients than many midwives. At present, medical education has advanced to a point where this has rapidly ceased to be true. Under present conditions, the most satisfactory way to abolish the more objectionable part of the midwife problem is to recognize her, control her, put her under educational requirements by the State, and bring these to such a point that only intelligent midwives can exist. This is part of the general improvement in medical education now going on throughout the country. Edgar states that in the Borough of Manhattan, there were, during last year, about 10,000 confinements in maternity hospitals as charity patients, and 7000 in their own home, a total of 17,000 free confinements. When the returns of births of the city of New York, for the past ten years are studied, it is interesting to note that during the past six years there has been a gradual but persistent decline in the number of births reported by midwives, until, in 1914, it reaches 37.6 per cent.

Much of this is due to the successful establishment of maternity dispensaries. That patients are willing to avail themselves of these institutions is shown by the experience of Edgar at Bellevue, after the establishing of the school for midwives; the number of patients in the service rapidly increased until in three years, 307 were attended in the school itself, and 630 in the town. In many cases midwives are employed by foreign women because the midwife is a woman; this could be obviated by encouraging graduate nurses from our training schools to make a specialty of obstetric work, and gradually to supplant the midwife. In the rural districts this would be a valuable procedure. Furthermore, the midwife frequently does domestic work in the household, often acting as housekeeper and cook. Experience shows, however, that foreign-born patients frequently employ a midwife for the first confinement after arriving in the country, and afterward go to maternity dispensaries or hospitals. Should competent midwives be no longer needed, they could still find employment as housekeepers. One of the circumstances which prevents the poor and those of very small means from having good obstetrical service, lies in the fact that there are very few low-priced rooms in hospitals. Edgar gives a summary of the educational work of the Bellevue School for Midwives which shows most satisfactory results, and may be referred to by all who are interested in the subject. So far as the supervision of the midwives goes, but four cities of the country, Philadelphia, Buffalo, Pittsburgh, and Providence, exercise efficient supervision over midwives. The licensing of these women presents difficulty unless there is recognized by the State an institution of authority competent to give a license. Edgar's experience in dealing with this problem is of special value in view of his connection with the Bellevue School for Midwives, and his wide experience in obstetrics. His conclusions, therefore, are of special interest. The midwife should have no place in modern medicine or surgery, but at present her elimination is impossible. She is, today, a necessary evil, attending about 40 per cent. of confinements in this country. Three professions have to do with the care of the parturient woman; the physician, the trained nurse, and the midwife, and no attempt should be made to perpetuate the last as a separate profession. The midwife should never be regarded as a practitioner. At best she is a nurse with sufficient knowledge to attend when necessary, normal deliveries. In rural and suburban districts, obstetric practice should be conducted by physicians and district trained nurses. The control of the education, licensing, and renewal of licenses should rest with the State Board of Health, or State Board of Education, the renewal of the license to depend upon the midwife's record for the year as demonstrated by supervisors from the local board of health. General improvement in medical education, the extension of dispensary maternity service, and the measures already described will reduce the ranks of the midwife, and render those remaining less a menace to the country, and pave the way for their final elimination. Baldy (*Amer. Jour. Obst.*, March, 1916) gives his experience in various methods in the conduct of obstetric practice. Admitting the existence of the midwife, the question arises, is she as efficient or more efficient than other agencies now in existence? As regards visiting maternity dispensaries, and medical school dispensaries, the senior students attached to these have had little or no experience, and do their work to gain experience. They compare unfavorably with some midwives. In comparison with the worst class of doctors, the statistics in Philadelphia show that patients are as well off, if not better, in the hands of midwives, than in the hands of doctors; the record showing 7 maternal deaths, and 365 fetal deaths in 12,000 cases. The question would be solved by the admission of all maternity cases to maternity hospitals. This is largely a matter of time and education, and is at present, impossible, because, for one reason, we have a continuous influx of foreigners added to our population. While the midwife cannot be eliminated at present, she can be educated and controlled, and to some extent, so can the public. In Pennsylvania a very considerable advance has been accomplished by Baldy in the matter of control and supervision. He believes that we should not educate new midwives, but allow a gradual and natural elimination. One of the most important agencies in securing the gradual elimination of the midwife is the requirement in Pennsylvania, that all hospitals shall furnish maternity service, and that each interne shall have at least six weeks service in obstetrics. Baldy summarizes his views to the effect that, theoretically, midwives should not exist. The time has not come when she can be eliminated, then those already in the field must be educated, and strictly regulated in practice. This will lessen their number in a way which even prohibition will not do. The education of new midwives or the admission of those educated abroad is of dubious value. Hospitals with maternity departments, and maternity hospitals should be developed to the point of highest efficiency, and patients encouraged to go to them. Lessening the number of midwives by the elimination of the unfit, refusing admission to any, or possibly but to a few of the new ones, and placing ample maternity service from hospitals at the disposal of the community, will do what prohibition cannot now accomplish in the elimination of the midwife. DeLee is strongly opposed to the midwife and believes it unnecessary that she exist. Recent medical graduates and younger physicians, with the establishment of dispensaries and maternity hospital service, have made the midwife no longer necessary. Her continuance can bring nothing but harm, and she should be abolished.

The Treatment of Puerperal Sepsis by Uterine Suction and Drainage.—Porritt (*Brit. Med. Jour.*, May 20, 1916) believes that when sapremia complicates the puerperal period, that an intra-uterine douche may convey infection into the peritoneum, causing rapidly fatal peritonitis. In 1 case he gave the patient an intra-uterine douche followed by violent abdominal pain and collapse, and death five hours later. Others have proved that fluid injected into the uterus makes its way into the tubes and peritoneum although very little force may be used for the injection. Where it is necessary to remove retained decidua from the uterus in cases of infection, the writer avoids the use of the curette and digital manipulation, and uses suction. A glass tube is passed into the uterus to which is attached a bulb, and by compressing the bulb a vacuum is created, and by allowing the bulb to expand, the contents of the uterus are drawn into the tube. In this manner retained septic material is removed with the least possible damage. He describes

2 cases in which this treatment was followed by the prompt recovery of the patient. He alludes to Gallant's experience (*New York Medical Journal*, October 10, 1914), where 252 cases of uterine infection were treated by continuous drainage with tubes. He describes a third case where the method of treatment was useless.

Pregnancy in the Tuberculous.—C. Norris (*Amer. Jour. Obst.*, June, 1916) has investigated at the Phipps Institute the course of pregnancy complicated by tuberculosis. He finds that pulmonary tuberculosis exerts very little or no influence in preventing conception, nor does it bring about abortion or premature labor in the average patient. Where the pulmonary tuberculosis is mild, one-fifth of the cases become worse during pregnancy or the puerperal period. Where the tubercular process is more advanced, two-thirds show decided increase. Tuberculous women should not marry because of the danger of increasing the tuberculous process. Pregnancy should be avoided unless the infection is a very mild one and has been quiescent for two years. In trying to estimate the result of pregnancy in a tuberculous patient, each case must be studied on its own merits. Before the fifth month of pregnancy the uterus should be emptied if the tubercular disease is active. Curettage during the first eight weeks, and later vaginal hysterotomy is indicated. Two-thirds of cases are better if pregnancy is interrupted. After the fifth month the case may go on if circumstances are favorable, induced labor being occasionally indicated and labor made as easy as possible. Tuberculous mothers should not nurse their children, and such patients should receive the best possible general treatment. Usually tuberculosis precedes pregnancy.

The Repair of Old Lacerations of the Genital Tract during the Puerperal Period.—Hussey (*Amer. Jour. Obst.*, June, 1916) reports 40 cases of laceration of the genital tract operated upon during the puerperal period. These comprise 31 old lacerations, 9 old and new tears of the perineum, 22 old lacerations, and 6 old and new tears of the cervix. The cervical injuries differed in severity, while the lacerations of the perineum were incomplete in 38, and complete in 2. One case was complicated by a vaginal cyst and hemorrhoids. The time selected for the operation varied from one to fifteen days after labor. In 5 operation was done within twenty-four hours after delivery; in 22, forty-eight hours after delivery; in 9, between the third and seventh days. Out of the 40 cases, 35 recovered without complications; 2 had rise of temperature on the day after operation; 2 had suture infection developing about the seventh day, relieved by removing the infected stitch. One patient had chill and temperature 102° F. which appeared at regular intervals, and was cured by quinin. There was primary union in this case. So far as the results of operation went, in 29 cases in which the cervix was repaired, there was primary union in 25; partial in 3, and no union in 1. On the perineum there was good union in 32; partial in 6; and none in 1. In 6 patients the uterus was retroverted when they left the hospital. In others the pelvic organs were in normal position. The average stay in hospital was between twelve and thirteen days. In operating, one must make allowance for the subsequent contraction of the parts, and the perineum and vulva must not be closed too tightly. The presence of lochial discharge did no harm. During the operation a gauze sponge placed in the vagina protects the wound, and close approximation of the edges protects the tissues later. So far as the interruption to nursing is concerned, the child was fed artifically during the day of operation, and nursed on the following day and afterward. In operating upon the cervix peculiar difficulties are found because of the relaxed and dilated condition of the parts. Hemorrhage may be excessive, and tissues may tear out when grasped by tenaculum forceps. In performing denundation, the tissues are soft and care must be taken not to excise too much force nor pull too strongly. It is recognized that the complete restoration of the genital tract to its normal condition can often not be secured by operation during the puerperal period, but many working women cannot cease work long enough to enter the hospital for secondary operations, and the opportunity must be taken to care for them during the puerperal period. Such operative work becomes not operations of choice, but those of necessity under existing circumstances.

Postmortem Cesarean Section.—Harrar (*Amer. Jour. Obst.*, June, 1916) reports 10 cases of postmortem Cesarean section in the practice of the Lying-in Hospital of New York. In 91,600 pregnancies at or near term, 50 women have died undelivered, most of them in less than an hour after entering the hospital. In 19 cases there was postmortem delivery. In 7 by version, resulting in 7 stillbirths, in 1 case the head of a living child was on the perineum and the child was delivered alive by a low forceps application. In 1 case version and extraction just after the death of the mother secured a living child. In 10 postmortem section was performed. When the conditions causing maternal death are studied, disease of the heart, placenta previa, rupture of the uterus, eclampsia, tuberculous meningitis, and cerebral hemorrhage were present Three of the children were stillborn, having probably died before the mother. Four were born with hearts beating feebly, but could not be revived. One died shortly after delivery; 1 on the sixth day, of pneumonia; 1 badly asphyxiated at birth left the hospital in good condition; and 1 crying spontaneously at delivery was discharged well. This gives 2 children living and in good condition out of the 10. In these cases the longest interval between the death of the mother and the birth of a living child was seven minutes. One delivered eight minutes after the mother's death gave a few feeble gasps and soon died, and 1 delivered twenty minutes after the mother's death made no attempt at breathing, although the heart was beating feebly. It is of the greatest importance that section be done as soon as possible after the mother's death. Efforts to resuscitate the child should be carried out as long as there is the slightest reason to hope for success. In the same number of the *Am. Jour. Obst.*, Whiteside, counsel to the Medical Society of the County of New York, gives the legal aspect of postmortem Cesarean section. In view of the present state of scientific progress, it would undoubtedly be considered culpable negligence if a physician were present when a woman pregnant at term died suddenly, if the physician did not immediately deliver the child.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA

Effect of Foreign Substances in the Peritoneal Cavity.—In view of the rather radical suggestions that crop out from time to time with regard to the introduction of more or less irritating chemical substances into the peritoneal cavity during the performance of a laparotomy in order to counteract infection or prevent subsequent adhesion formation, some experiments recently reported by Cubbins and Abt (*Surg., Gynec. and Obst.*, 1916, xxii, 571) are of considerable interest. These investigators studied upon animals the effect of iodin, ether, and various oily substances, all of which have at various times been advocated for use in clinical work, with the following results: *Iodin.* This was used in 3.5 per cent. alcoholic solution. It was found to destroy the endothelium immediately, and if used in excess of 4 ounces to a 20-pound dog caused death within forty-eight hours. About half the dogs receiving not more than this amount recovered if there had been no traumatism to the intestines, but all were very sick for several days. Out of 20 animals only 2 lived for three months; these both showed at autopsy firm fibrous adhesions or bands between the intestines. In one instance 4 ounces of iodin were mixed with 1 ounce of pus for thirty minutes, and then introduced; death occurred within twenty-four hours from diffuse peritonitis. It seems evident from this series of experiments that iodin must be considered an intense irritant to the peritoneum, and that it will probably produce firm fibrous adhesions with or without manipulation of the intestines. It appears to favor rather than inhibit bacterial action. *Ether.* One ounce placed in the peritoneal cavity of a dog was found to have an intense anesthetic effect, and would produce death within three to five minutes if introduced into the peritoneum of an already anesthetized animal. Ether poured into the abdomen of a semi-conscious animal causes a temporary awakening, with cries of pain, generally followed by deep anesthesia, though not always. No analgesia was noticed following recovery from operation. Ether was found to be not nearly so irritating as the 3.5 per cent. iodin, but it did seem to have a marked effect in lowering the resistance of the peritoneum to infection, as when any manipulations whatever were carried out not under all aseptic precautions, and ether was introduced, the animals invariably died in three or four days with violent peritonitis, this series comprising 25 animals. In a series of thoroughly aseptic operations, plus ether, about half the animals lived; at autopsy later, about half of these were found to have adhesions, the other half being free. *Vaselin.* After the introduction of this substance the animals were always violently sick, two dying in forty-eight hours from intussusception. One dog, which lived three months, showed a matting together of the bowels, with lumps of vaselin between the loops. It appears that it is an intense irritant to the peritoneum, and is absorbed very slowly, if at all. Abolene and lanolin acted entirely similarly to vaselin. *Russian oil.* This was used in 16 animals. It has no apparent irritating effect. In 1 case, 4 ounces were introduced under aseptic technic, and after six weeks the oil was found to be present in practically the same quantity as when introduced, but there was no inflammation. In other instances, white cakes of inspisated oil were found on the spleen and other organs. If the intestines were handled with gloved hands during operation, and then paraffin oil was smeared on, there was no appreciable prevention of adhesions. *Olive oil.* This was found to be relatively non-irritating, but very slowly absorbed. In 1 case the oil was found throughout the abdominal cavity six weeks after 1 ounce had been introduced under aseptic conditions, no adhesions being present, except to the abdominal wound. No prevention of adhesions after manipulation could be demonstrated in most cases, though in 2 out of 10 such experiments adhesions were not found at subsequent autopsy. From these investigations it would appear evident that while none of the substances studied can be considered of any definite value, several of them are distinctly dangerous, and should never be employed clinically. It is probable that in the cases reported as recoveries following the use of one or the other of these substances, the recovery has taken place in spite of, rather than because of, the material introduced into the perineal cavity.

Syphilis of the Female Generative Organs.—A most exhaustive study of this subject, to which in the past surprisingly little attention has been paid, has been made by GELLHORN and EHRENFEST (*Amer. Jour. Obst.*, 1916, lxxiii, 864) for the recent symposium on the subject by the American Gynecological Society. Covering considerably more than 100 pages, their paper considers the subject from all standpoints; in addition to presenting a very considerable number of carefully studied original cases, the authors have collected in brief from practically all the available literature, and have based their conclusions largely upon this as well as upon their own observations. In reviewing a work of this extent, it is possible to present only a very brief summary of the author's most important conclusions; the subject is of such importance, however, that the attempt to do this appears justified, in the hope that it will stimulate those interested to refer to the original publication. Gellhorn and Ehrenfest do not consider as by any means demonstrated the commonly accepted belief that syphilis is commoner among men than among women; at least they believe that latent syphilis prevails more in women than in men. Not every disease in a syphilitic woman is syphilitic in nature, but the presence of the syphilitic infection will often exert an influence upon co-existent diseases, so that it constitutes a gynecologic problem in the widest sense. With regard to the individual organs involved, the authors find that definite lesions of the vagina are rare. Primary chancres may, however, often be overlooked, because the parchment-like induration persists but a short time, and there are no definite symptoms, such as pain or vaginal discharge. Likewise secondary lesions, such as macules or papules, have no symptomatology of their own, and are usually discovered only accidentally during a specular examination. Tertiary lesions, when present, almost always originate in structures surrounding the vagina, rather than in that organ itself. They do not exhibit any characteristic symptoms, and are probably of exceedingly infrequent occurrence. The primary chancre of the cervix presents, on the other hand, the best known and most common type of syphilitic affection of the female genitalia, but it, likewise, does not give rise to any noteworthy clinical symptoms. Under normal conditions the primary lesion heals very quickly or becomes transformed into an inconspicuous erosion. Secondary cervical lesions manifest themselves in the form of macules, papules, and ulcerations, these probably representing three successive stages in the development of a lesion caused by accumulations of the spirocheta pallida in the squamous epithelium of the cervix. The organism can easily be demonstrated in the secretion from any of the three forms, thus explaining the great infectiousness of secondary lesions. These also heal quickly, as a rule, and energetic specific treatment always results in resolution in a very short time. A fairly large number of tertiary cervical lesions are on record; the essential form of these is the gumma, which generally undergoes necrosis and ulceration. The process may involve the vagina or extend into the cervical canal. Bleeding or mucopurulent discharge is usually present, but no pain. The lesions may heal spontaneously, and disappear very quickly under specific treatment, but local treatment is altogether useless. With regard to syphilitic lesions of the body of the uterus, our knowledge is extremely meagre. Primary and secondary manifestations have never as yet been observed. A few instances of gumma of the uterine wall are on record, and one of gummatous involvement of the endometrium. Unless syphilitic lesions of the uterus have been overlooked in the past, it must be assumed that this organ possesses a relative immunity, for the uterus more than any other internal organ, is exposed to direct infection. The tubes appear likewise to be immune. While it seems possible that they may be the seat of luetic involvement, no definite lesions have been described, and spirochetes have never been found in them. Various changes in the ovaries, such as simple enlargement, syphilitic oöphoritis, tertiary sclerosis of the ovary, ovarian gumma, have been described as expressions of luetic infection of these organs, but in practically no instance has positive proof been furnished that such alterations are actually due to a local luetic process. The authors do not consider the fact that a condition of metrorrhagia, or less commonly amenorrhea, may disappear after specific medication, a proof of a syphilitic ovarian lesion. In no instance have spirochetes been demonstrated in the ovaries of adults. Syphilis of the pelvic cellular tissue does undoubtedly occur, however, appearing in the form of a diffuse gummatous infiltration, usually leading to a wrong diagnosis of malignancy. Specific treatment produces in these cases an amazingly rapid improvement of an apparently hopeless condition. The question of the relation between syphilis and metrorrhagia is taken up at some length by Gellhorn and Ehrenfest. They do not believe that metrorrhagia is necessarily a syphilitic manifestation, nor that it is the result of any local condition in the uterus. They believe firmly in the ovarian origin of all uterine hemorrhages save those caused by abortion, polyps, and carcinoma. They doubt, however, that syphilis causes specific lesions in the ovary, as has already been pointed out, but they do believe that syphilis, by infection of the entire organism, produces, in some cases, disturbances in the function, but not in the tissue of the ovary, and that these ovarian disturbances cause menstrual disturbances in the form of hemorrhages. The rapid improvement under antiluetic therapy is a strong point against the theory of definite ovarian lesions, as these could hardly be influenced so quickly. Moreover, the combination of lues and gonorrhea is exceedingly frequent; the lesions following the latter condition, and also those following the frequent abortions that occur in syphilitics may in many instances be the underlying factors of the metrorrhagia. The authors declare themselves, however, thoroughly in accord with those writers who recommend a trial with specific therapy before radical treatment is decided upon for all cases in which a uterine hemorrhage is not definitely explained by local findings. In conclusion, the authors call upon the gynecologists, who have profited in the past by the pioneer work of the dermatologists in the realm of syphilis, to come forward and contribute their share, as there are still many mooted questions which the gynecologist is preëminently fitted to solve.

OTOLOGY

UNDER THE CHARGE OF

CLARENCE J. BLAKE, M.D.,

EMERITUS PROFESSOR OF OTOLOGY IN THE HARVARD MEDICAL SCHOOL, BOSTON.

Traumatic Rupture of both Drum Heads from Hand Grenade Explosion.—G. Alexander (*Monatschr. f. Ohrenheilk.*, xlix, 8). The patient, a lieutenant, aged twenty-eight years, had good hearing up to the time of the explosion of a hand grenade three paces distant; there was no loss of consciousness, but an evident decrease of hearing in the right ear with a subsequent sensation of discomfort, and of passage of air outward through the ear, lasting two days; a few days later there was evident decrease in hearing in the left ear also. Following the explosion there was a general, continuous circulatory tinnitus and occasional headache, both temporal and occipital, with slight occasional dizziness. There was no discharge from the ears and the later otoscopic examination showed in the right ear a perforation the size of a millet seed in the anterior inferior segment of the drum head and in the left ear almost total destruction of the drum head and absolute retraction of the malleus; the edges of the perforations were congested and flecked with blood and, in the left ear, the torn remnants of the membrane were reflected inward upon the tympanic wall. The hearing in both ears was nearly normal, the right internal ear reacted normally in all respects, the left showed marked decrease in duration of hearing by bone conduction, but the hearing in that ear for the upper tone limit was normal; the static labyrinth reacted normally on both sides.

The treatment consisted in closure of the external canals with antiseptic gauze, renewed daily, with rapid diminution of the size of the perforations, that on the right side being entirely healed at the end of a week and the left one month later, when the patient was discharged with very nearly normal hearing. Similar ruptures of the drum head, as the result of explosion, with implication of the internal ear are comparatively rare. In this case the rupture was the result of a forcible explosion at close range, and in both sides ideal healing resulted, on the left side the remnantal portions of the drum head served to reconstitute the membrane by the intermediate growth of cicatricial tissue. The decrease in the hearing by bone conduction on the left side would indicate either a traumatic affection of the middle ear or trauma of the meninges, or both, and this persisted up to the time of the patient's discharge from observation. In confirmation of this observation Urnbantschitsch reports a case in which the patient was thrown down by the explosion of a bomb several meters distant, and on arising found himself extremely hard of hearing in the right ear; examination showed a rupture of the drum head revealing the whole of the inner tympanic wall. Three weeks later there was spontaneous closure of the opening by cicatricial union of the remnants of the membrana vibrans and a later examination showed no sign of the rupture and the hearing was perfectly normal. In the use of hand grenades the conditions under which the patients are exposed to the explosion have a determinable influence upon the effect, in illustration of this the author cites 3 cases of such injury. All of the patients in question were possessed of practically normal hearing. In the first instance the explosion occurred within a confined space, in an artillery hut, while in the other 2 cases the explosion took place in the open. In the first instance the patient and his companions were thrown either to the floor or against the walls of the enclosure. Both auricles were burned by the flame of the resultant gases and there was subsequent distortion as the result of perichondritis. The patient was unconscious after the shock; whether this was the result of a concussion or the poisonous effect of the gases in a circumscribed space cannot definitely be determined. The right drum head was slightly thickened, the left drum head was normal, and the middle ear sound-transmitting apparatus had not been injured by the explosion, notwithstanding which fact there was a considerable impairment of hearing in both ears, similar to that previously observed in cases of poisoning by carbon dioxide. In the second case the patient was thrown to the ground by the simultaneous explosion of a shrapnel overhead and to his right, but did not lose consciousness. This experience was followed by headache, loud subjective noise in the right ear, and decrease in hearing; there was no vertigo. The patient was sent first to the relief station and then to the hospital, and an examination ten days later showed him to have prompt pupil reaction, no motor disturbance, and reflexes normal. In the right ear there was a sharply defined perforation in the centre of the drum head of the size of a millet seed and a tympanic hematoma; the left drum head was perfectly normal, In the third case the patient stood within two paces of a 10 cm. field gun, but too far forward. As a result, upon the firing of the gun, he was thrown to the ground, with an outflow of blood from the right ear but without loss of consciousness, and for the next eight days had a peculiar sensation on the right side of his head upon sneezing and blowing his nose, accompanied by pain in the right ear, but no vertigo and no subjective noise. Examination showed an oval perforation in the anterior portion of the drum head, pars flaccida, and the posterior superior quadrant of the membrane vibrans being markedly congested and swollen. In the left ear there were merely slight catarrhal changes in the tympanum. The hearing in the right ear was much decreased and in the left ear was perfectly normal. In both cases the ear which was nearest the sound source was the one affected, and in both there was a characteristic depreciation in the hearing for the upper tone limit. Gaupp says in regard to the effect of hand-grenade explosions that they comprise four factors: namely, the air pressure, the influence of poisonous gases, the mechanical shock, and the psychic shock. The impairment of hearing in these cases is, as a rule, only an element in the production of a picture of a psychoneurosis, the impairment of hearing coming from two sources: the one a central cerebral disturbance and the other a condition incident to the effect of the concussion upon the peripheral organ of hearing. These components are found to vary considerably in the degree of their influence, and in a number of patients who lost both hearing and speech following exposure to hand-grenade explosions, two were restored to hearing and two to both hearing and speech after two months of electrical application and energetic suggestive treatment. In reference to the indirect injury to the ear the most common injury to the internal ear was that due to the effect of heavy blows upon the skull or to concussion due to missiles, without demonstrable injury, directly, of the petrous bone. Of 200 cases carefully examined there were 85 of indirect injury to the internal ear. In almost all cases of either traverse or penetrative wounds of the facial portion of the skull the inner ear was affected; in the majority of cases of glancing or gutter wounds of the skull the internal ear was found to functionate normally both as regards hearing and equilibrium. The glancing and gutter wounds of the mastoid process, however, were productive of a very marked participation of the internal ear.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,
PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

JOHN F. ANDERSON, M.D.,
FORMERLY DIRECTOR OF THE HYGIENIC LABORATORY, PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Vitality of the Cholera Vibrio in the Waters of New York Bay.—Gelarie (*Med. Rec.*, February 5, 1915, p. 236) states that, since about 70 per cent. of all epidemics of infectious diseases like typhoid and cholera are caused by the use of polluted water, either for drinking or washing purposes, an examination of the waters of New York Bay is very important, especially as there may be vessels at anchor there which have come from countries where cholera is prevalent. Since it is known that the dejecta of convalescent cholera patients may contain cholera vibrios forty-eight days after recovery and dejecta are usually thrown into the bay from vessels, the question has arisen as to whether or not the cholera vibrio would survive or die if placed in the waters of New York Bay. Two factors should be considered as to the survival of cholera vibrio in such water: first, the sudden increase in osmotic pressure due to the large amount of salt in the water and, secondly, the overgrowth of the cholera vibrio by other organisms in the water. To determine the influence of the first factor, water was collected from the centre of the bay, autoclaved for 200 minutes, inoculated with cholera from an eighteen-hour slant of a cholera strain isolated a few months previously in the Philippines and plated at once. Similar platings were made after twenty-four hours, forty-eight hours and at twenty-four-hour intervals until the twenty-sixth day. There was a constant increase up to the eighth day showing that the increase in osmotic pressure has no apparent influence on them. To study the influence of the associated microörganisms in the unsterilized waters of the bay, water was collected from the centre of the bay, inoculated at once with cholera from a twenty-four-hour agar culture, then inoculated on Dieudonne's medium and other differential media. A given number of loops were inoculated on the plates and the resulting colonies counted after incubation of from twenty-four to forty-eight hours, the cholera colonies being differentiated from the others by their color. The count showed that the number of the cholera vibrios in native bay water decrease rapidly while the number of other colonies increases. In the other experiment to study the influence of the second factor, a similar method was employed, *i. e.*, a certain amount of cholera suspension was added to 200 c.c. of water in an Erlenmeyer flask which was kept at room temperature in the dark. At intervals, a certain amount of the water was plated and the number of colonies, which developed, counted. To the water remaining in the flask, an amount of peptone, sufficient to make up a 1 per cent. solution, was added. After sixteen to eighteen hours incubation, plates were made from the peptone on alkaline agar and on Dieudonne's medium, and characteristic or suspicious colonies fished, inoculated on agar slants and subjected to the agglutination test. Four strains were used, a strain which had been cultivated in the laboratory for two years, a strain from the Museum of Natural History, an Egyptian strain and an Austrian strain. In general, the vibrios had been passed one or more times through a guinea-pig before being used. Only a sixteen- to eighteen-hour culture was used. Tests were made to determine the comparative viability of the various strains when the nature of the water and the number of vibrios varied. In the sterile bay water containing 149,500 vibrios of the laboratory strain, the vibrios lived 154 days; in the native bay water, containing the same amount, they lived only 21 days; in sterile tap water, they lived 18 days, and in native tap water 3 days. When 4,000,000 vibrios of the

Museum strain were added, it was found that at the end of 285 days, the vibrio were still alive in sterile bay and ocean water, while in the native bay and ocean water, they lived only 7 days. When 60,000,000 vibrios of the Egyptian strain were added, they survived for 47 days in the native bay water. These results show that the life of the vibrios in native water is short, probably due to the unfavorable action of the water bacteria upon them and that the longevity depends on the strain employed, the nature of the water and the quantity of organisms involved. A test to ascertain the comparative viability of B. coli communis and the cholera vibrio showed that B. coli disappeared within 3 days whereas the cholera vibrios were still alive after 285 days. The conclusion states that, although the foregoing experiments show that cholera vibrios do not multiply in native bay water, yet they do survive for from 7 to 47 days and the mere presence of them in water demands greater precaution.

Etiology and Laboratory Diagnosis of Smallpox and Chickenpox.—(*Journal of Lab. and Clin. Med.*, January, 1916.) The presence of granules in the vaccine vesicle was recorded by Sacco, and later Chauveau showed that the active principle of vaccine virus was contained in these granules. Although a number of observers have made studies of the bacteria in the vaccine vesicles, no one has been able to produce vaccinia lesions by animal inoculation with a pure culture of any of them. DeWaele and Sugg isolated from persons dead of smallpox a streptococcus which was agglutinated by the serum of smallpox in dilutions of 1 to 800 and from chickenpox vesicles, they isolated a streptococcus which although readily agglutinated by chickenpox serum, was not agglutinated by the serum of smallpox. Therefore, they announced the specificity of these organisms and suggested the agglutination test as a means for the differential diagnosis of smallpox and chickenpox. In 1891 Copeman, and in 1882 other observers, came to the conclusion that vaccine virus would retain its activity even if it was rendered free of the usual bacteria by mixing with 50 per cent. glycerin. This fact suggested a protozoan origin for the disease. Guarineri gave the name cytoryctes to certain extranuclear bodies which he found in the epithelial cells of smallpox vesicles and Councilman, Brinkerhoff and Tyzzer confirmed the presence of such bodies, and maintained that they were the true parasites of smallpox and vaccinia. They also described a second form within the nucleus of the epithelial cell in smallpox only. Tyzzer described bodies enclosed in the nuclei and cytoplasm of the epithelial cells of the chickenpox vesicles and, associated with them, he found a division of the nucleus and an enlargement of the epithelial cells. However, he was unable to produce lesions with chickenpox material in the corneal cells of the rabbit. The newly discovered cytorcytes were not generally accepted as the causative agents of smallpox and their parasitic nature was denied. They were thought to be irritation bodies as similar staining bodies were found in the cornea after inoculation with India ink. Salmon showed that the staining reaction of the cytoryctes corresponded to that of the nuclei of migrating leukocytes and Foa denied their parasitic nature on account of a non-protozoan morphology and because analogous forms found in sheeppox would not pass through the filter which allows the passage of the sheeppox virus. Another observer, Van Prowazek, considered the cytoryctes a hyperproduction of nuclear material due to a stimulation by the smallpox organism. By some investigators, the inclusion bodies in the epithelial cells of the chickenpox vesicle were considered analogous to the cytorcytes while others found them to possess different staining reactions and a different structure. The majority of investigators have been unable to inoculate with chickenpox vesicle contents, but Kling succeeded in inoculating healthy children with fluid from a fresh chickenpox vesicle and out of 31 inoculated, during an epidemic, only 1 developed febrile chickenpox. These facts show that the clinical similarity of chickenpox and mild smallpox is confirmed by a similarity of the reaction of the epithelial cell to the invasion of either organism as well as a similarity in the protection afforded by vaccination and varicellation, while the fact that a smallpox immune child could be varicellated indicates that the two diseases are not modifications of the same process. Various experimenters have attempted to pass the smallpox organism through the Berkefeld filter and their experiences indicate that the organism is contained in some type of surrounding substance and will not pass through until this is removed by digestion, grinding or the action of solvents. In any case, the activity of the virus is reduced by filtration. The most comprehensive study of the morphology of the smallpox organism has been made by Belin who found from his studies of pus from smallpox vesicles: (1) Motile coccoid forms less than 0.5 micron in diameter which were agglutinated by the serum of smallpox immunes. (2) Similar forms within the cells. (3) A very few large oval bodies sometimes as large as 2.0 microns. (4) Spirochetes occurring early, sometimes containing bodies similar to the free coccoid forms. He also states that he obtained all these forms from serum broth to which had been added small particles of rabbit skin inoculated with vaccine virus, and claims that reproduction of the organism took place in this medium. This work has been repeated with similar results. A bacteria-free vaccine has been secured by Steinhardt by means of the dialysis of commercial glycerinated virus through collodion sacks, by Foret by killing the bacteria by shaking with ether and by Foster by bubbling ether through a long column of vaccine pulp. Noguchi has recently succeeded in restoring the virulence of the etherized virus of Foret which does not maintain its potency. *Differential Diagnosis of Smallpox.* Because of the existence of border-line cases, which present difficulty in diagnosis, a laboratory method would be of value. The following methods have been suggested: (1) Microscopic examination of the vesicle contents. Tyzzer considers the presence of large polynuclear cells characteristic. (2) Excision of the skin lesion and histological examination. (3) Inoculation of the cornea of a rabbit with the vesicle contents. The epithelial cells are examined for inclusion bodies. (4) Inoculation of a well vaccinated person with the contents of the vesicle. Jenner noted that a sudden efflorescence was produced on the application of smallpox material to the scarified skin of persons who had suffered from smallpox, variola inoculata or vaccinia. (5) Inoculation of vaccinia-immune rabbits with the contents of the vesicle chickenpox inoculation has no effect on rabbits; but rabbits, sensitized by vaccination with vaccine virus give a marked intradermal reaction with smallpox vesicle contents in from twenty-four to forty-eight hours.

Torula Infection in Man.—A large literature has grown up in regard to the lesions produced in human beings by organisms of the blastomycosis group. These cases are of importance not alone by reason of the particular infection, but because of the similarity of the lesions to those of tuberculosis. A study of cases in Peter Bent Brigham Hospital has afforded Stoddard and Cutler (monograph No. 6 of Rockefeller Institute) an opportunity to give the problem of the relationship of the lower fungi forming the group of blastomycosis attention. By the study of two cases in the Peter Bent Brigham Hospital, which presented unusual lesions of the brain and spinal cord, the problem of the relationships of the lower fungi forming the group called blastomycosis, was brought to notice. Attempts to classify the blastomycoses have resulted in indefinite conclusions. Coccoidal granuloma has been found to be distinct from the other types called blastomycoses because it never buds in tissues but sporulates while the blastomycotic organism buds but never sporulates. The coccidioidal organism varies more in size and produces lesions more nearly like tuberculosis, the infection spreading more often by the lymphatics than by the blood. There is a distinction between the true yeasts and torula on the one hand and the oidium on the other hand. In the latter group, to which the ordinary blastomycetes belong, there is both budding and hyphæ production. A summary of these differences will be given later. A study was made of 10 cases of so-called systemic blastomycosis with brain lesions and, of these, 6 showed either skin or subcutaneous tissue lesions as the principal features. The other 4 cases all had brain lesions of such a nature as to cause the predominating clinical symptoms throughout the disease. In all 4 of these cases, there were lesions in the brain containing large numbers of yeast-like bodies, surrounded by a gelatinous matrix, and the clinical and pathological symptoms were entirely distinct from the cases of blastomycosis producing skin or subcutaneous tissue lesions. A study was made of these sections and bacteriological characteristics of Frothingham's case of torula infection in a horse and great similarity to the latter 4 cases, numbers 1, 2, 9 and 10, noted. Pure cultures of the torula organism were injected into animals and brain lesions, identical with the brain lesions of cases 1, 2, 9 and 10 were produced in rats, adding to the evidence that these were true cases of torula infection. The study of other cases of systemic blastomycosis without brain lesions led to the conclusion that Buschke's cases of true yeast infections formed a group distinct from either of the two just discussed, which is a very small group, only two undisputed cases having been found. The clinical and pathological characteristics show that, although it resembles the oidium type in that its principal lesions are cutaneous or subcutaneous with internal lesions in the bones, lungs, kidneys and spleen and is like the torula group in that it has less attractive power for polynuclear leukocytes, sometimes has an adventitious capsule and is known to produce brain lesions in animals, yet it differs in some respects from either group. Culturally, it is differentiated by its spore production. A careful study was made of two cases of torula infection in their clinical, pathological and bacteriological characteristics. In both cases, there were severe brain lesions containing many organisms, in the first case in the form of large, resting cells, and, in the second case, in a more active form, in which budding cells were present. Similar meningeal inflammatory tissue was found in both cases, and in the second case there were lesions in the lungs, bronchial lymph nodes, liver and spleen, in all probability due to the action of the same organism. In both cases, there was a close resemblance of the lesions with caseation to tuberculosis. In the cases of torula infection studied, fever was observed with one exception, the white count was ordinarily not increased and organisms were found in the spinal fluid. The symptomatology of the cases resembles closely that of brain-tumor and there were also points of similarity with chronic diseases of the nervous system such as syphilis. From the knowledge gained by this study of the organisms, a more accurate classification of the diseases formerly called blastomycosis can be made. 1. True yeast infection, produced by an organism which reproduces by budding and produces endospores in culture. It is only slightly pathogenic for animals. 2. Torula infection, produced by a yeast-like organism, distinguished from yeasts by the absence of endospore production and by its greater pathogenicity for animals. 3. Oidiomycosis, caused by an organism which reproduces by budding in tissue and which forms a mycelium in cultures. There is no endospore production. In localization, it affects especially the skin and subcutaneous tissues. A series of animal inoculations were performed, three cultures being used, one isolated from a human case of cutaneous blastomycosis, one from a human case of coccidioidal granuloma and one from Dr. Frothingham's case of torula infection in the horse. In the experiments on dogs, torula lesions only were present in the brain and kidneys and no lesions were present as a result of the other organisms, showing that the dog is relatively resistant to the 3 groups of organisms. In the rabbit experiments, the oidiomycosis injection produced no lesions, the coccidial injection resulted in an abscess at the site of the injection while in the intraperitoneal injection with torula, lesions were found in the kidney, brain and meninges. The experiments on guinea-pigs showed no lesions with oidiomycosis and with torula only peritoneal nodules were produced by intraperitoneal injection. Two of the guinea-pigs inoculated with the coccidoidal organisms had lesions, the one inoculated subdurally having a brain lesion. Lesions were produced in mice with the coccidoidal and torula organisms but not with the oidiomycosis. When rats were inoculated with torula, a general infection with lesions in the meninges, brain and cerebellum were produced. These experiments showed all the variations in lesions and organisms seen in the torula cases and thus helped to show the correlation of all the human cases as cases of torula. The agglutination tests made with these animals were of no diagnostic value. The cultural characteristics are in brief as follows: reproduction by budding, no gas production with sugars, no spore production, abundant growth on potato, agar or dextrose agar. In tube inoculation a smooth, pasty, slightly shiny, thick, yellow layer is formed. There is no liquefaction of media. In bouillon there is a slight cloudiness but no surface growth. The diagnosis of torula infection is sometimes difficult because a number of factors work to conceal its identity. Infections may occur during life without any noticeable symptoms. Lesions may appear at autopsy but if in the healed stage, the organisms will be practically indistinguishable and the picture will be that of a slightly typical tuberculosis. The factors which will aid in the recognition of torula infection are: discovery of early lesions in internal organs before the parasite is destroyed; realization of the finer points of difference from tuberculosis; complete brain examination; cultures especially on carbohydrate media at room temperature; and injections of fluids and cultures into white mice intraperitoneally with a microscopical examination following especially of the brain. Torula infection is a chronic disease and in regard to the localization of lesions and organ resistance, the animal experiments show the tendency toward the production of a general infection from intraperitoneal injections with special involvement of the nervous system. On the whole, the respiratory tract seems to be the most probable point of entrance of the disease and the path of distribution is, in many cases, through the lymphatics to the blood stream. The parasite is adapted to various conditions by the small, actively budding organisms and the resistant spheres for unfavorable conditions. The torula starts by the passage of a small torula into the tissue while in a phagocytic cell from the blood stream. It multiplies within the cell and destroys the cell, liberating the organisms, which multiply and produce a gelatinous material which surrounds them. Phagocytic mononuclear or giant cells take them up and the organisms develop within them, destroy the cell and all are set free. The surrounding tissue is partly dissolved or pushed away and strands of connective tissue often form about the gelatinous capsules with each space containing an organism.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

JOHN McCRAE, M.D., M.R.C.P.,

LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL;
SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT,
BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL
VICTORIA HOSPITAL, MONTREAL,

AND

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH,
PITTSBURGH, PA.

Tissue Reactions in Experimental Hypercholesterinemia.—The part played by the cholesterin molecule in metabolism has of late received much attention. The increased cholesterin of the blood occurring in various skin diseases as well as chronic wasting diseases has been well demonstrated in man. Its significance and manner of disposal is still not entirely clear. Some light has been thrown upon the subject through the experimental work of the Russian School headed by Calatow upon the manner of cholesterin absorption and its primary metabolism by particular tissues. Much of this has recently been confirmed by McMeans (*Jour. Med. Research,* 1916, xxxiii, 481). In his studies, rabbits were used and fed with known cholesterin amounts by the stomach tube. In this way the animals received large quantities of cholesterin, either in solution in olive oil or in a combination with sodium oleate. The latter was found to give the most marked responses and it appeared that the cholesterin was more easily absorbed when used in combination with the oleate. Although the hypercholesterinemia could be fairly rapidly induced, the tissue changes developed more slowly. He found that there was a certain sequence in which the tissues dealt with the cholesterin. A temporary hypercholesterinemia is rapidly disposed of probably by way of the liver. It would appear that the adrenal is an important organ for the handling of excess cholesterin in the blood stream. A similar activity was found in the corpus luteum. The liver and spleen may each serve as organs for storage when the hypercholesterinemia is long induced. The storage of cholesterin by the liver appears to occur only when the excretion by the bile ducts is insufficient to maintain the proper blood balance. The tissue reactions in all of these organs appear to primarily involve the endothelial structures. A hyperplasia of this type of cell was found in a majority of the organs. This hyperplasia occurring in the spleen gave rise to a microscopic picture simulating the Gaucher spleen. Other endothelial reactions were also observed in the arteries and in the interstitial tissue of the kidney. This latter response is a very interesting one which at the present time cannot be definitely explained.

Experimental Studies of Foreign Body Inflammation.—Herzog (*Ziegler's Beiträge,* 1914, lxi, 377) has particularly given attention to the tissue reactions following upon the injection of sterile foreign materials. Guinea-pigs and rabbits were used. The author studied the reactions following the injection of kaolin into the peritoneum. A low grade inflammation was induced. The cellular exudate appeared to consist of cells migrating from the blood stream as well as cells developing *in situ* from the fixed tissue elements. Of the latter the adventitial cells appeared to be most active. These cells are commonly found surrounding capillaries and small bloodvessels. They are held to be of endothelial origin, having been derived from the lining of the bloodvessels. These endothelial cells may assume many shapes and are often difficult to distinguish from immature connective tissue. These adventitial cells, the author believes, can give rise to different types of parent cells from which lymphocytes, granular leukocytes and giant cells may be derived. Most important appears to be the property of developing lymphoblasts from which the various types of lymphocytes may be developed. By this means, also, the author believes that the newly formed lymphocytes may proceed to the development of granular mononuclears and then to the acidophile leukocyte. The author claims to have observed the various stages in the transformation of basophilic lymphocytes into eosinophile leukocytes. The author believes that no differentiation may be made between the tissue mast cell and the leukocytic mast cell. Not only could these cellular reactions be observed in the peritoneum, but also in the omentum and bowel mucosa. The giant cells which are so often seen about foreign bodies may have their origin from the peritoneal lining, large wandering cells or fibroblasts. These giant cells were observed to form both by fusion of several cells or through a process of incomplete amitosis. The study in general indicates a wide tissue origin of a great number of wandering cells which, by many, have been considered distinctive for the hemopoietic organs. Many of the ideas expressed support the view of Marchand in whose laboratory the work was done.

Complement Fixation Reactions of the Bordet-Gengou Bacillus.—Cultural methods alone have been insufficient to distinguish the Bordet-Gengou bacillus from the influenza group of organisms. Bordet-Gengou found that the complement was not bound when an influenza antigen was in contact with the serum of pertusis convalescents. This work was confirmed by Arnheim, he found that rabbit immune sera will bind the complement in the presence of their homologous antigens. Wolstein obtained similar results and found that there was no cross fixation of complement with the influenza antigen and the Bordet-Gengou antigen in the presence of the heterologous sera. Several authors have found that the fixation of complement test was a practical method of differentiating the Bordet-Gengou bacillus from the influenza bacillus. Olmstead and Povitsky (*Jour. Med. Research,* 1916, xxxiii, 379) reported many of these tests upon 14 strains of the Bordet-Gengou bacillus, 4 atypical types and 9 belonging to the influenza group. The authors prepared antigens from the cultures of each organism. Immune serum was obtained by inoculating rabbits with the various bacteria, tests being made at intervals to determine the potency of the rabbit serum during the course of treatment. A great number of animals were used in the preparation of the sera and much work carried on in testing homologous and alien strains. The authors found that the complement fixation test was a very useful adjunct for the differentiation of the typical and atypical B. pertussis. It is quite infrequent to have cross complement fixation but its occasional occurrence suggests a relation between some members of the groups. The typical B. pertussis is quite distinct from the B. influenza.

Morphological Changes in Tissue with Changes in Environment: Gastric Mucous Membrane Implanted into Intestine.—A number of authors have called attention to the structural changes of the mucous membrane in the vicinity of a gastro-enterostomy. Cade noted the change in the gastric glands at the site of the anastomosis so that they resembled the glands of the pyloric region. Harvey also observed similar changes but found that the new morphology was transient and that the normal mucosa was restored after a period of six months. Smith (*Jour. Med. Research,* 1916, xxxiii, 337) carried out a series of experiments wherein metaplastic changes resembling those described by Cade and Harvey were noted in the gastric mucosa following implantation into the intestine of flaps taken from the fundus of the stomach. Dogs were used in all (12) experiments. A plastic operation was undertaken so that a flap of stomach wall with intact vascular supply was implanted into the large or small intestine. The animals were killed at intervals from four days to fifteen months. The author found that the implanted tissue showed a disappearance of the chief and parietal cells normally found in the fundus. In place of these, a type of cell developed resembling that normally found in the pyloric region. These newly formed cells are of an indifferent character containing no secretory granules but giving a reaction for mucus. At times, only small areas of the implanted tissue showed the cellular changes. The author points out that a number of cases have been described in which the epithelium of the fundus of the stomach had lost its normal character and assumed the structure of the intestinal epithelium or fundus of the stomach. These findings have been offered as examples of heterotopia resulting from embryonal disturbance or for others they have served as examples of metaplasia. From an analysis of his own materials, Smith believes that these areas are the result of metaplasia brought about through the altered state of the stomach and its secretions.

Old Age in Relation to Cell Overgrowth and Cancer.—The changes occurring in tissues in old age are believed by many to influence the appearance of certain tumors. For the most part, these observations have been confined to man, although latterly the extensive studies upon cancer in mice show a similar principle underlying the incidence of tumors in them. The particular reason that the age of cells and tissues prepares them for the development of new growth is explained by different authors in various ways. GOODPASTURE and WISLOCKI (*Jour. Med. Research*, 1916, xxxiii, 455) found a general and constant tendency to benign and malignant tumors in old dogs. It was not unusual to find multiple tumors especially of glandular tissues. They examined 15 old animals, and in each instance demonstrated one or more new growths. The liver and adrenal showed the presence of tumor in all but one instance. It was remarkable how widely the tissues of the body are involved in primary neoplasma in old dogs. The changes present in each organ were fairly constant, with the presence of the same type of tumor. Benign or malignant growths were found in the liver, gall-bladder, adrenal, spleen, prostate, ovary, thyroid, stomach, testis, pancreas, thymus, salivary, sebaceous and mammary glands, hypophysis, parathyroids, adipose and connective tissue, and bloodvessels. The list is remarkable, and the frequency of multiple tumors in the same animal, sometimes as many as eleven organs showing new growths, is of great interest. The liver, spleen and pancreas are most frequently affected. Only one tumor (from the adrenal) showed extensive metastases in the liver.

Studies upon Xanthelasma Associated with Chronic Icterus.—A clear distinction between xanthoma, xanthelasma, and pseudoxanthoma has not been made and it is questionable whether we are prepared at the present time properly to classify them. It was believed that the first of these processes was of the nature of a spontaneous tumor arising from a peculiar lipoid containing cell. As, however, no clear distinction could be made between the small aggregations of these cells and the larger masses which displaced the surrounding tissue, the question has arisen whether these cell groups differ only in size of mass rather than in the nature of their formation. The presence of xanthelasma has been shown to be associated with diabetes, icterus, nephritis and other bodily disturbances. A common manifestation in xanthomatous processes is the presence of a doubly refractile lipoid contained within large endothelial cells. SCHULTE (*Ziegler's Beiträge*, 1916, lxi, p. 570) described another case of localized xanthelasma associated with icterus. The condition was found in a man suffering from cancer of the bile papilla. The bile duct was almost occluded with stagnation and infection of bile, in its ramifications through the liver. Scattered through the liver substance in the vicinity of the bile ducts and Glisson's capsule were many yellow areas clearly demarcated from the liver substance. The microscopic examination showed a cirrhosis of the liver with xanthomatous tissue in the trabeculæ. Similar masses were also seen in the capsule of the spleen and in the skin of the right elbow. The tumor tissue was similar in all situations. The author enters into a long discussion of the possible mode of origin of these cell masses. It would seem that a process of irritation or injury is a factor in the various situations where the lesion is found. Besides this, however, it is suggested that a condition of hypercholesterinemia has much to do with these tissue changes. The recent work which has been done on cholesterin metabolism indicates a most varied pathological state under which the storage and utilization of cholesterin may be altered. Under not a few conditions is it found that the metabolism of cholesterin is altered with the result of its unusual appearance in the blood. To this increased blood cholesterin content, a response occurs in a particular type of tissue or cells of many organs whereby temporary storage is undertaken. The development of this tissue, composed of endothelial cells, leads to a pathological reconstruction in various organs. These have the appearance of xanthoma masses. Aschoff even refers to the Gaucher spleen as belonging to the xanthomatous process.

Localization of Pulmonary Emboli.—Many studies upon the mode of production and the localization of pulmonary emboli have been made since Virchow carried on a series of experiments in which foreign bodies were placed in the jugular vein. He observed the localization of the emboli in the branches of the lower lobes of the lung. Kretz carried on a similar series of experiments using a variety of substances to serve as embolic masses. He found that the inoculation of foreign materials into the ear veins of rabbits, led to their localization in the pulmonary arteries of the upper lobe and the posterior part of the lower lobes. A unique experiment wherein chloroform was injected into the veins, gave him similar results. The use of chloroform was valuable, he claimed, in that it brought about the death of the animal within a minute after injection, before any of the material was driven through the capillaries of the lungs. Kretz pointed out that when oils are used, not a little of the oil passes through the capillaries of the lung to pass onward into the systemic arteries, and probably return to the lung by the inferior vena cava, and thus become distributed to new areas in the lung. Georgi who carried on a similar series of experiments in rats and rabbits was unable to support the contention of Kretz. Ribbert claimed to have demonstrated a focal distribution of the blood stream, but not in the sense of Kretz. Ribbert believed that individual parts of the blood flow in venous channels maintained their relative positions fairly accurately and were constantly distributed to particular areas. Schoenberg (*Centralbl. f. Pathol.*, 1916, xxvii, 73) repeated many of the experiments of the various authors, avoiding those methods of which question has been raised by some observer. A suspension of bismuth was found most satisfactory as none of it passed through the lung capillaries. The passage of the bismuth emboli along the vessels could be watched with the use of the roentgen-rays. Eighteen rabbits were used. It took about six seconds for the particles to pass from the ear vein to the right auricle, and two seconds to pass through the right ventricle. Schoenberg was unable to confirm the constant particular distribution of the pulmonary blood in the lungs, as was claimed by Kretz.

Further Observations on the Pathology of Cardiac Dropsy.—Bolton (*Jour. Path. and Bact.*, 1916, xx, p. 290) has on a previous occasion reported upon experiments on this subject. Dropsy was induced by constricting the pericardium or narrowing one of the venæ cavæ. These observations were only obtained during the first twenty-four hours after operation. In the present study the observations were prolonged over several weeks after the inferior vena cava alone had been narrowed. The method, he states, is fairly simple when performed on cats. He found that ascites appeared a few hours after the obstruction had been produced. It gradually increased up to a certain quantity and then disappeared, apparently through the establishment of vascular anastomoses. The obstruction to the blood led to congestion of the tissues behind the constriction and the output of lymph was considerably increased. Within the peritoneum it was difficult to estimate the secretion of lymph as a continuous absorption was taking place. The author also studied the variation, the blood-pressure and the hemoglobin content in these experiments. In estimating the intake of fluid and the excretion of urine there was evidence of retention during the period of edema. The results are complicated in that the circulatory changes are associated with varying portal stasis including the liver which at times is sufficient to deplete the general circulation. When the inferior vena cava is narrowed to three-fifths its normal diameter an immediate fall in the mean arterial pressure results. The author recognized various stages in the development of ascites depending directly upon the changes occurring in the areas where passive congestion was induced.

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ORIGINAL ARTICLES

THE DIAGNOSIS OF POLIOMYELITIS.

By Josephine B. Neal, A.B., M.D.,
CHIEF, MENINGITIS DIVISION, DEPARTMENT OF HEALTH, NEW YORK CITY,

AND

Phebe L. Dubois, M.D.,
FORMERLY CHIEF OF MENINGITIS DIVISION, BUREAU OF LABORATORIES, DEPARTMENT OF HEALTH, NEW YORK CITY.

The Meningitis Division of the Department of Health was established six years ago in order to afford to the physicians of the city of New York expert assistance in the diagnosis and treatment of meningitis. Since 1910 we have held consultations in over 1300 cases, presenting a great variety of meningeal conditions. These have included tuberculous meningitis, purulent meningitis of all kinds (meningococcic, pneumococcic, streptococcic, influenzal, staphylococcic); meningism in a variety of diseases, especially pneumonia and other acute infections in children; many rarer conditions, such as brain abscess, brain tumor, syringomyelia, etc.; and also about 70 cases of poliomyelitis occurring before the incidence of the present epidemic. When we add to them the number of frankly paralytic cases which were diagnosed by the attending physician without expert aid and the number of cases which we may reasonably assume escaped diagnosis altogether, we may arrive at some idea of the prevalence of poliomyelitis between the periods of epidemics.

It is evident that these rather numerous sporadic cases are dangerous foci of infection, and it is probably from such as these that our epidemics take their origin. They are the smouldering embers from which the sparks of conflagration may be disseminated at any time to inflammatory materials nearby. Those children born between the periods of epidemics are most susceptible to the disease; hence it is among these that the greatest morbidity occurs.

Dissemination. Animal experimentation has conclusively demonstrated that the virus of poliomyelitis is discharged in the secretions of the nose, throat, and alimentary tract of patients suffering from the disease and in the secretions of the nose and throat of individuals in intimate contact with these patients.

In 1911 Kling, Petterson, and Wernstedt first succeeded in inoculating monkeys with the virus obtained in washings from the nose, throat, and alimentary tract of subjects who had died of poliomyelitis. Since then the experiment has been many times successfully repeated with washings obtained from living patients and also from their attendants. Dr. Zingher and the authors obtained washings from the nose and throat of an abortive case two weeks after the incidence of the sickness. With these we produced typical poliomyelitis in monkeys. In sections of the brain from one of these monkeys a few globoid bodies similar to those described by Flexner and Noguchi were found. A report of this work appeared in the *Jour. Am. Med. Assn.* for January 3, 1911.

Careful studies of epidemics in recent years have led to the conclusion that the mode of transmission of the disease is by actual personal contact rather than through intermediary means such as dust, flies, and insects. The Stomoxys calcitrans seems now to have been quite eliminated as a factor in the dissemination of poliomyelitis, though at one time much importance was attached to the part which this insect was thought to play in epidemics. It is conceivable that the common house fly may act as a passive carrier, as it does in typhoid fever; but its disease-bearing potentialities are strictly limited to this passive role.

Many important epidemiological studies have been made in recent years. One of the most interesting of these is that of Kling and Levaditi, who carefully investigated a small and definitely circumscribed epidemic occurring in 1911 on two little islands in the Bay of Stätboken, off the coast of Sweden. Because of the limited number of persons living on these islands, and the ease with which their movements could be followed, it was possible to trace clearly the probable transference of the virus from case to case. In this respect the report of this epidemic is unique.

A careful study of recent epidemics also brings out the fact that while, not uncommonly, two or more children of one family may be attacked simultaneously by poliomyelitis, it much more frequently happens that but one case will occur in a household consisting of several children of susceptible age, all of whom may have been equally exposed to the contagion. A similar phenomenon is seen in epidemic meningitis. It is only to be explained on the theory that those who escape possess a natural immunity to the virus of poliomyelitis. The number of susceptible children must also be proportionately small. We do not understand either the mechanism of this immunity or the reason for it. It has, however, been clearly demonstrated by means of the Schick test in the case of diphtheria infections, and analogy gives rational grounds for the belief that it also occurs in poliomyelitis.

Flexner has shown that the virus of this disease retains its virulence when subjected to high summer temperatures, to drying, or to the action of weak chemicals which destroy ordinary bacteria. It possesses, therefore, considerable resistance, and this fact should be borne in mind with every case. Bright sunlight readily destroys the germ.

To most of the laity, and to many physicians as well, poliomyelitis is known as a disease characterized by a frank, flaccid paralysis, its last stages being always mentally associated with the usual orthopedic brace. It may be well, therefore, to consider at this time those more atypical or abortive cases in which paralysis is transitory or entirely absent, because these, so usually unrecognized, are the most potentially dangerous.

In his monograph on acute poliomyelitis, Wickman presents the following classification of its varieties which is self-explanatory.

1. Spinal poliomyelitic form.
2. Form resembling Landry's paralysis.
3. The bulbar or pontine form.
4. Encephalitic type.
5. Ataxic type.
6. Polyneuritic type.
7. Meningitic type.
8. Abortive type.

While this classification is quite comprehensive it is perhaps somewhat complex for clinical use, and a simpler classification is that of Peabody, Draper, and Dochez, which presents three groups, namely:

1. Abortive types or non-paralytic (cases presenting no paralysis at any time).

2. Cerebral group (embracing involvements of the upper motor neuron with resulting spastic paralysis).

3. Bulbar spinal group (presenting lesions of the lower motor neuron with flaccid paralysis).

It is maintained by some authorities that poliomyelitis is a general infection and that symptoms of its effects on the central nervous system are entirely secondary in nature, when not absent altogether. It has even been suggested that paralytic cases may be in reality the atypical ones. Those holding this view would, in times of epidemics, diagnose as poliomyelitis cases presenting merely respiratory or gastro-intestinal symptoms, particularly if a case of frank paralysis exists in the same family at the time. When we consider the prevalence of gastro-intestinal disturbances in children, more especially during the summer season, such a conclusion is hardly tenable, unless corroborated by characteristic findings in the spinal fluid.

Personal experience inclines us to believe that these changes in the spinal fluid commonly accepted as diagnostic of poliomyelitis do not exist independently of some definite clinical manifestation of involvement of the central nervous system. It does not seem possible that a disease accompanied by an inflammatory reaction in the central nervous system and meninges of sufficient severity to produce changes in the spinal fluid could fail at the same time to afford definite clinical evidences of nervous involvement. Therefore, in the past, we have made it a rule to consider the possibility of poliomyelitis, and to perform lumbar puncture only in those cases presenting symptoms referable to the nervous system, such as hyperesthesia, Koenig's or the spinal sign, altered reflexes, stiffness of the neck, MacEwen's sign, etc. In the absence of these signs and in the presence of a normal clear spinal fluid we have always definitely excluded poliomyelitis.

When any of these signs are not present we have usually considered a lumbar puncture unjustifiable. In the few cases where we have performed it the fluids have been normal. The present epidemic may afford the opportunity to throw additional light upon the question by means of lumbar puncture in cases without meningeal symptoms, and also by means of animal inoculation.

Incubation Period. The incubation period of poliomyelitis has not been definitely determined. It is considered by Wickman to be from one to four days and by Müller to be from five to ten days, averaging about a week. This corresponds to the incubation period of the disease as experimentally produced. Some observers, as Peabody, Draper, and Dochez, describe a true prodomal stage which they define as the period before the appearance of paralysis. As it is well known that many cases of poliomyelitis remain entirely free from all paralysis, it would seem unwise to date the incidence of the disease, even in the paralytic form, from the appearance of paralysis. We are, therefore, not justified in speaking of a true prodromal stage. There is, however, a type of onset described by Kling, Levaditi and others which we have also sometimes observed. In this the disease is ushered in by somewhat indefinite symptoms of an intestinal, coryzal, or anginal nature. A remission of from one to several days then occurs, to be followed by return of all symptoms and, usually, by an accompanying paralysis.

Symptoms of Onset. The initial symptoms are much the same in all types of the disease and they may be quite as severe in the abortive as in the paralytic forms. While the onset may rarely be insidious, in the vast majority of cases it is very abrupt. Fever is probably the most constant, as well as usually the first, symptom. As a rule it is high and of comparatively short duration, falling by crisis or by lysis. Next to fever the most frequent symptom is a pronounced hyperesthesia or diffuse tenderness over the whole body. This is, perhaps, most marked in the legs and along the spine. There is also a decided drowsiness and the patient manifests great irritability when disturbed. Headache and vomiting are common. Constipation or diarrhea may be present, in our own experience, the former being more frequent. Retention of urine sometimes occurs, and this possibility should be constantly borne in mind. Convulsions, delirium, and spontaneous pains in the neck, back, joints, and limbs are other symptoms which may appear. Meningeal symptoms are very pronounced in a fairly large portion of cases. These are anteroposterior stiffness of the neck; Kernig's sign or the spinal sign of Peabody, Draper, and Dochez; MacEwen's sign, or change in the percussion note over the lateral ventricles due to distention with fluid. The reflexes may be exaggerated, but usually they are diminished or abolished. The pupillary reflex is, as a rule, retained. Following these symptoms paralysis may develop, most commonly appearing about the second day, though it may be delayed as late as the second week.

I. Abortive or Non-Paralytic Type. In the cases of the abortive type the above-mentioned symptoms may subside quickly —that is within a few days—without any evidence of paralysis or even of any weakness; or the paralysis or weakness may be transient only; or the condition may persist for two or three weeks, presenting a clinical picture which is most difficult to differentiate from tuberculous meningitis. But very often in these abortive cases all symptoms are much more indefinite than the above description would indicate. Therefore in the presence of an epidemic an unexplained temperature, especially if accompanied by general hyperesthesia, is sufficiently suspicious to warrant a lumbar puncture. This procedure not only assists materially in making a diagnosis, but practically always it markedly relieves the symptoms arising from meningeal irritation.

II. Cerebral Types (involving the upper motor neuron with spastic paralysis). Under this heading we may perhaps place those cases called polioencephalitic by Wickman. While, in our experience, examples of involvement of the upper motor neuron have not been uncommon, we have seen no single case presenting a spastic paralysis. In certain subjects with severe convulsions we have found the reflexes to be exaggerated, but evidences of spastic paralysis have been entirely wanting.

We have also occasionally found cases, somewhat resembling tuberculous meningitis, of a protracted duration, and presenting unmistakable symptoms of cerebral involvement, such as drowsiness, irritability, etc. But in these cases the reflexes have been sometimes diminished or lost instead of being exaggerated, as would be expected with cerebral irritation. Though realizing the difficulty of accurately classifying them, we have been in the habit of calling these polioencephalitic. We believe the true cerebral type of poliomyelitis to be exceedingly rare. No cases have fallen within our personal experience.

A very unusual manifestation of poliomyelitis is blindness. Our meningitis division has seen two such cases, one in the present epidemic. In the first case the vision was restored at the end of about three months. The second is a quite recent case and the blindness still persists.

III. Bulbospinal Type (with flaccid paralysis). Cases of this type are readily recognized. Therefore, they have long been considered as classical examples of poliomyelitis, and descriptions of them are found even in our older text-books. Hence they call for but little discussion here.

In the present epidemic a fairly large number of cases of this type have presented a rapidly ascending variety of paralysis, involving the muscles of respiration and ending with death. Some of these, when seen late, after pulmonary edema has developed, have been diagnosed as bronchopneumonia.

Examples of the bulbar type of paralysis, with difficulty in speaking and swallowing, are not uncommon in this epidemic. Some have, occasionally, been diagnosed as croup. Facial paralysis has also been quite common. As a rule it is not accompanied by the involvement of other muscles.

Differential Diagnosis. In the first twenty-four to forty-eight hours after its onset, poliomyelitis must be differentiated from the early stages of epidemic meningitis or mild purulent meningitis, and also from a meningism accompanying pneumonia or other infection. The clinical pictures presented by the above-mentioned diseases are quite similar, and it is in distinguishing between them that the examination of the spinal fluid affords us the most reliable information.

When seen a week or more after the onset, cases of poliomyelitis, especially if presenting cerebral symptoms, must be distinguished from tuberculous meningitis.

The procedure which we find to be our most reliable and valuable aid in the recognition of poliomyelitis is the examination of the spinal fluid. In poliomyelitis this fluid is usually clear. Very rarely it may be slightly cloudy in the early stages. It often shows a good fibrin web formation. The reduction of Fehling's solution is prompt. There is a slight or moderate increase of albumin and globulin and also of the cellular elements. As a rule, 80 per cent. or more of the cells are mononuclears. In examining such fluids we have frequently observed the presence of large mononuclear cells which we believe to be in a measure characteristic of poliomyelitis. Those poliomyelitic fluids which are cloudy present a polymorphonucleosis which may run as high as 90 per cent., but which we usually find to be about 60 per cent.

Two rare types of spinal fluids sometimes occur in poliomyelitis when the hemorrhagic process has been more than usually severe. The first of these is of the true hemorrhagic character, the red blood cells being evenly diffused throughout the field. When collected in successive tubes the specimens are all homogeneous, showing no change in the intensity of the hemorrhage. This serves to differentiate it from bloody fluids obtained by the accidental puncture of a vein.

Evidence of an older hemorrhage occurs in the second of these rarer fluids, which, having a characteristic yellow color and coagulating spontaneously, illustrates the so-called syndrome of Froin. These fluids occur in other conditions, and are therefore not pathognomonic of poliomyelitis.

In early cases of *purulent meningitis* the spinal fluid shows a varying degree of cloudiness, except in very rare instances, when it may be clear. A greater increase in albumin and globulin is usually found here than occurs in poliomyelitis, with a poorer reduction of Fehling's solution. The cells in these fluids of purulent meningitis are 90 per cent. or more polymorphonuclears, and the etiological organism is always found except in the mildest cases. In certain mild cases of meningitis—probably of the epidemic variety—the meningococci may never be positively demonstrated in the fluid. In purulent meningitis due to other organisms these practically always appear later. In one instance only we have seen a clear fluid from an early case of epidemic meningitis of about eighteen hours' standing. Although the cellular reaction was so slight the meningococcus was demonstrated to be present in the fluid by smear and culture.

The fluid in *meningism* is increased in amount, but is practically normal in character.

The fluid in *tuberculous meningitis* most nearly resembles that of poliomyelitis. It is practically always clear with a cellular increase consisting largely of mononuclears, though in very acute cases it may be distinctly cloudy with an excess of polymorphonuclears. The number of cells per cubic centimeter is usually greater than in poliomyelitis; the increase in albumin and globulin is more marked, and the reduction of Fehling's is not so good.

In rare instances when clinical signs are confusing and when the results of the cellular examination and chemical analysis are indefinite, and it is impossible to demonstrate the tubercle bacillus in the fluid, a positive diagnosis must wait upon the results of animal inoculation.

A detailed study of the spinal fluids of poliomyelitis examined at the Research Laboratory of the Department was made by Dr. H. L. Abramson, of the meningitis division. This was published in the *Am. Jour. Dis. Children*, November, 1915.

Another laboratory method of slight diagnostic value may be mentioned here, the so-called neutralization test. In this, serum from a suspected case in the stage of recovery is mixed with a known fatal dose of an active virus. These are incubated and later injected intracerebrally into monkeys. Failure of the disease to develop indicates that the virus has been neutralized. This test, however, does not furnish conclusive evidence of poliomyelitis, for sera from those known to have been free from a recent attack of the disease have sometimes successfully neutralized the poliomyelitic virus.

An exhaustive study of the blood picture was made by Peabody, Draper, and Dochez. It was shown that there existed a varying increase in leukocytes and a polymorphonucleosis. This is characteristic of so many other diseases that it affords little aid in diagnosis.

So far no specific treatment for poliomyelitis has been successfully developed. The intraspinal injection of the serum of convalescent patients has been tried, especially by Netter of Paris, but up to the present time no conclusive results have been obtained. In view of the rapidity with which the virus produces paralysis after the onset of symptoms, the possibility of a measure that will prevent its development seems too much to hope for. It has been suggested that the serum of convalescent patients may aid in the rapidity and extent of the recovery from the paralysis, though it would seem that after the very early stage the patient's own antibodies would far outnumber those in the sera of cases of some months or years' standing. It would seem, therefore, that the greatest hope of success in combating poliomyelitis lies perhaps in a prophylactic vaccination. Work is being done in this direction, and the present epidemic may be productive of results of value.

ON THE VALUE OF THE QUANTITATIVE ESTIMATION OF DISSOLVED ALBUMIN IN THE GASTRIC CONTENTS IN THE DIAGNOSIS OF CANCER OF THE STOMACH.[1]

By Julius Friedenwald, M.D.,
PROFESSOR OF GASTRO-ENTEROLOGY, UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE AND COLLEGE OF PHYSICIANS AND SURGEONS, BALTIMORE,

AND

Richard F. Kieffer, M.D.,
RESIDENT PHYSICIAN, UNION PROTESTANT INFIRMARY, BALTIMORE.

Wolff and Junghans[2] were the first to report a special method for the estimation of the soluble albumin in the gastric extract which they claim of great value as an aid in the diagnosis of gastric cancer. More recently Smithies[3] has confirmed the value of this test.

From a study of a large series of examinations, Smithies draws the following conclusions.

1. When carefully performed and interpreted the Wolff-Junghans test for demonstration of dissolved albumin in gastric extracts was positive or suspicious in 80 per cent. of our series of gastric cancer. In this series it was a more constant finding in gastric extracts than were absent free HCl, the presence of lactic acid, and the glycyltryptophan test; it was rather more constant than tests for occult blood, and the demonstration of gastric motor inefficiency. It was not so constant in its manifestation as the demonstration of organisms of the Boas-Oppler group or the increase in the formal index.
2. In extragastric malignancy, gastric syphilis, and nephritis the Wolff-Junghans test is inconstant.
3. In the differentiation between the malignant and non-malignant achylias the Wolff-Junghans test when interpreted in connection with other clinical and laboratory data is of considerable value. Positive reactions are rarely obtained in the achylias of primary anemia, simple achylia gastrica, and simple achylorhydrias when such are unassociated with gastric motor inefficiency.
4. Simple gastric and duodenal ulcers, especially when accompanied by pyloric stenosis or gastric atony, may give confusing responses to the Wolff-Junghans test.
5. The presence of blood in the gastric extracts may be a factor in the production of certain atypical positive tests.

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[1] Presented at the Meeting of the American Gastro-Enterological Association in Washington, May 8, 1916.

[2] Berl. klin. Wchnsch., May 29, 1911, and March 18, 1912; Med. Klinik, March 24, 1912.

[3] Am. Jour. Med. Sc., May 1914, and Cancer of the Stomach, p. 245.

The increase in albumin is probably due to the presence in gastric cancer of an enzyme which is formed by the growth of the cancer cells, which is markedly proteolytic in action. On this account the aspirated test meals are very rich in soluble albumin in the malignant achylias, while in the benign achylias but small amounts are obtained.

The test is carried out as follows: The gastric secretion is filtered and then diluted with distilled water, $\frac{1}{10}$, $\frac{1}{20}$, $\frac{1}{40}$, $\frac{1}{100}$, $\frac{1}{200}$, and $\frac{1}{400}$. The precipitating reagent utilized is as follows

Phosphotungstic acid (pure), 3 c.c.
Hydrochloric acid (concentrated), 10 c.c.
Alcohol (96 per cent.), 200 c.c.
Aquæ dest. q. s. ad., 2000 c.c.

Mix and keep in a glass bottle with rubber stopper in a cool place. One c.c. of this reagent is floated on the surface of the six dilutions of gastric juice already mentioned. A pearly white ring at the junction of the gastric juice with the reagent denotes a positive reaction. According to Wolff and Junghans, positive reactions occurring in dilutions of $\frac{1}{10}$, $\frac{1}{20}$, $\frac{1}{50}$ are present under normal conditions, while when still present in dilutions of $\frac{1}{100}$, $\frac{1}{200}$ and $\frac{1}{400}$, malignancy is indicated.

In conducting the reaction it is quite important to test the gastric secretion immediately upon the withdrawal, for if it be allowed to stand aside for a short time, solutions of greater dilution than those noted are quite apt to produce a more intense reaction. Rehfuss, Bergeim and Hawk[4] have also pointed out by means of their method of fractional analyses the importance of giving test meals on a completely empty stomach, inasmuch as residues are often present, which may produce exaggerated reactions. It is also important, according to these investigators, to warn the patient against the swallowing of salivary or bronchial secretion while the test meal is still present in the stomach, inasmuch as such substances are quite apt to occasion an excessive protein content.

Smithies reported his observations with the Wolff-Junghans test in 215 cases of gastric cancer. In 141, or 65 per cent., the test was positive; in 29, or 13 per cent., it was suspicious. It is evident, therefore, that in 170, or 78 per cent., cases of cancer it was positive or suspiciously positive; in 45, or 21 per cent., it was negative.

The value of this test has also been demonstrated by Einstein,[5] Rolph,[6] Katznelson[7] and others. Trallero[8] studied 80 cases according to this method, examining the stools and having roentgen-ray examinations made. He disregarded all contents containing blood. The highest albumin figures were observed in carcinoma, though in certain instances normal amounts were noted. In certain cases of chronic gastritis large quantities of albumin were observed. Trallero believes that there may be a contamination with saliva, which he has found to produce amounts of albumin ranging from 160 to 320, and which seems to vitiate the conclusions of others and rob the test of much of its value.

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[4] Jour. Am. Med. Assn., September 12, 1914.

[5] Med. Klinik, March 24, 1912.

[6] Med. Record, May 10, 1913.

[7] Russky Vrach. March 28, 1915.

[8] Deutsch. med. Wchnschr., July 9, 1914.

Our experience with the Wolff-Junghans reaction extends over a series of 173 cases. The method of carrying out the test was practised according to the plan already described. A positive reaction was only noted when the reaction was still present in dilutions of $\frac{1}{200}$ or $\frac{1}{400}$ and suspicious in dilutions of $\frac{1}{100}$.

Of the 173 cases 67 were benign achylias and 106 cases of gastric cancer. Of the 67 benign achylias 9, or 13.5 per cent., gave positive or suspicious reactions, while 58, or 86.5 per cent., gave negative reactions. Of the 106 cases of undoubted cancer of the stomach, 89, or 83.9 per cent., gave positive or suspicious reactions, and 11, or 16.1 per cent., gave negative results. Our experience corresponds with that of other observers in that this test is of little or no value in the presence of free HCl in the gastric contents. All cases of cancer containing free HCl have therefore been excluded from this series.

Inasmuch as the presence of blood interferes with the test, gastric secretions containing this substance were likewise discarded. Of the 89 cases in which positive reactions were obtained, 18 were early cases; reaction was positive in 13, or 72.2 per cent.; while the remaining 5 did not present this reaction until later in the course of the disease.

It is of interest to note the occurrence of this reaction in comparison with other findings. Of the 106 cases of gastric cancer, 89, or 83.9 per cent., gave positive reactions. In all of these cases free HCl was absent, lactic acid was present in 70, or 78.6 per cent. Oppler-Boas bacilli were observed in 68, or 76.4 per cent., occult blood in the stools in 78, or 87.6 per cent.; dilatation of the stomach with retention occurred in 38, or 42.6 per cent.

In a consecutive series of 130 cases of cancer of the stomach in which 115, or 88 per cent., presented an absence of free HCl the Wolff-Junghans reaction was present in 95, or 82 per cent.

The test was made in 6 cases of cancer in other abdominal organs in which the stomach was not involved; of these the pancreas was affected in 3 instances, the bowel in 2 instances, and the liver in 1. All of these cases presented an absence of free HCl. Of these, 3, or 50 per cent., gave negative reactions, 2, or 33 per cent., suspicious, and 1, or 17 per cent., a positive reaction.

An examination of 8 cases of peptic ulcer was made as to the amount of soluble albumin. In all of these cases there was an absence of free HCl. In 2, or 25 per cent., the reaction was positive, in 1, or 12 per cent., suspicious, while in 5, or 62 per cent., it was negative. In the 2 positive cases pyloric stenosis with dilatation was present. In 14 cases of chronic gastritis the reaction was positive in 1, or 7 per cent., suspicious in 1, or 7 per cent., and negative in 12, or 85 per cent.

In 45 cases of simple achylias the reaction was positive in 2, or 4 per cent., suspicious in 2, or 4 per cent., and negative in 41, or 91 per cent.

Five cases of gastric carcinoma were studied according to the fractional method of Rehfuss, Bergeim, and Hawk with special reference to the Wolff-Junghans reaction for soluble albumin. The results of these cases were compared with those of 5 cases of simple achylias similarly examined.

The conclusions arrived at agree with those of the above-named authors, namely, that in simple achylias the gastric secretion shows a moderate amount of soluble albumin during the entire period of digestion, the protein curve remaining low and conforming in a marked degree with the acid curve, while, on the other hand, in carcinoma the protein curve diverges quickly from the acid curve, considerable amounts of albumin being usually present within three-quarters of an hour, the quantities being markedly increased to positive reactions within an hour to an hour and a half.

From a careful study of our own cases, together with the cases of others, we feel that we are justified in concluding that the Wolff-Junghans test is of great value as an aid in the diagnosis of certain forms of gastric carcinoma, and when taken in conjunction with the other signs of the disease may be of the greatest diagnostic help. The test is, however, only useful in the diagnosis of the disease, when there is an absence of free hydrochloric acid in the gastric contents, and then only when the question of even traces of blood can be eliminated, and in the absence of all retained food residue or of swallowed saliva or sputum.

The test has its greatest significance in the diagnosis between simple and malignant achylias. Positive reactions are rarely observed in simple achylias, while they are frequent in cancer.

In fractional analyses in simple achylias the acid and protein curves followed each other closely, while in malignant conditions there is a marked divergence between the protein and acid curve.

Positive reactions occurring under normal conditions, or in simple achylia gastrica appear, in dilutions of $\frac{1}{10}$, $\frac{1}{20}$, $\frac{1}{50}$, while when still present in dilutions of $\frac{1}{100}$, $\frac{1}{200}$, $\frac{1}{400}$ there is marked evidence toward malignancy.

The test is positive in at least 83 per cent. of gastric cancers, presenting an absence of free HCl and in 72 per cent. of early cases. It occurs almost as frequently as the absence of free HCl in this disease (89 per cent. absence of free HCl to 82 per cent. positive Wolff-Junghans reactions). It is more frequent than the presence of lactic acid (presence of lactic acid, 78 per cent. positive Wolff-Junghans test 83 per cent.), or the Oppler-Boas bacilli (presence of Oppler-Boas bacilli, 76 per cent. positive Wolff-Junghans test, 83 per cent.).

A positive reaction rarely occurs in malignant growths in the abdomen not involving the stomach; in gastric ulcer, except in cases associated with stenosis and dilatation or in chronic gastritis or simple achylias. While the test is of value as an aid in the diagnosis of gastric carcinoma, it is only then of significance when taken in connection with the other signs of the disease, and thus is an additional means of aiding in the detection of a disease frequently most difficult of diagnosis.

THE PHARMACOLOGY OF EMETIN.

By Emil J. Pellini, M.D.,

and

George B. Wallace, M.D.,

New York.

(From the Department of Pharmacology, University and Bellevue Hospital Medical College.)

In recent years a considerable amount of interest has been attached to the alkaloid emetin. This has been due in the first place to the striking results obtained with it in the treatment of amebic dysentery, and secondly to its present wide-spread use in pyorrhea alveolaris. In connection with its use in dysentery it is interesting to note in the fifth edition of Cushny's *Pharmacology*, 1910, that while ipecacuanha is accepted as being almost a specific, doubt is cast on the part played by emetin, and in fact, mention is made of a "de-emetinized" ipecac said to act equally well. Meyer and Gottlieb in their *Experimental Pharmacology*, second edition, 1911, state that the effective factor is the tannic acid contained in ipecac. The careful work of Rogers,[1] however, has established definitely that the curative effects of ipecac are due entirely to the emetin it contains, and that emetin may rightfully be classed as a specific for the amebic type of dysentery.

The use of emetin in pyorrhea alveolaris is of much more recent origin and is due especially to the work of Bass and Johns,[2] who have assumed that the Entamoeba buccalis is an important factor in this disease, and is affected by emetin in the same specific manner as the Amoeba histolytica. Following their publications and those of Smith and Barrett[3] and others, emetin has achieved a new prominence, and has become very extensively employed in the treatment of pyorrheal infections. In this at-present popular use of the drug, scant attention is paid to other and deleterious actions it may possess, and it is not at all improbable in view of the somewhat unusual toxic effects it may induce in animals, that considerable damage has already been done through injudicious dosage or too long-continued administration. For this reason it seems desirable to examine into the pharmacology of emetin, to confirm observations already brought out by experimental means, and to add such additional facts as may seem of importance.

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[1] British Med. Jour., 1912, No. 1, 1424; 1912, No. 2, p. 405; Dysenteries, Oxford University Press, 1913.

[2] New Orleans Med. and Surg. Jour., 1914, lxvii, 456; Jour. Am. Med. Assn., 1915, lxiv, 553; Alveolodental Pyorrhea, Philadelphia and London, Saunders Co., 1915.

The literature on the pharmacology and clinical effects of emetin is fairly extensive, but contains comparatively few publications based on careful experimental work. In the earlier work the preparation used was not pure emetin, but a mixture of emetin and cephaelin. The two alkaloids are closely related chemically, however, and their actions in general are the same, the chief differences being that cephaelin is more irritant locally, more apt to damage the kidney, and less toxic to the heart. This has been made clear by the work of Lowin,[4] who obtained the two alkaloids in pure form. His experimental results with pure emetin differ in no appreciable degree from those of earlier investigators, notably Podwyssotzki,[5] so that it is safe to assume that the latter made use of a mixture in which the emetin action was the predominant one.

The main toxic effects of emetin, as shown by practically all of the earlier workers, are exercised on the gastro-intestinal tract and on the heart. Magendie and Pelletier,[6] in 1817, demonstrated that the emetic action of ipecac was due to its alkaloid content, and further that the alkaloid, regardless of whether given by mouth or injection, produced a definite inflammatory reaction along the mucous membrane of the alimentary tract. Duckworth,[7] in 1871, found that toxic doses caused a cardiac paralysis which came on suddenly and quickly caused death of the animal. Doses not large enough to induce cardiac paralysis, produced no changes in the circulation. Other investigators have elaborated on these actions and have added further ones.

The local irritant action of emetin has been long recognized. Duckworth mentions that apothecaries in pulverizing ipecac root are very apt to have marked irritation of the conjuctiva and nasal mucous membrane. Lowin found that a 1 to 500 solution of emetin applied to the conjunctival sac produced a violent irritation. He states, however, that an irritation of subcutaneous tissues following injection does not occur, and concludes from his experiments that emetin is a specific irritant to mucous membranes. The emesis produced by emetin has been generally considered as an expression of the irritation of the gastric mucous membrane. Subcutaneous injection, it is true, causes emesis, but the dose necessary is not smaller than that given by oral administration, nor is the time required for vomiting to occur noticeably shorter. Foulkrod[8] claims to have found emetin in the stomach after subcutaneous injections, and looks on this as additional evidence of the peripheral action in emetin emesis. Hatcher and Eggleston,[9] on the other hand, have recently reported experiments in which emetin caused definite vomiting movements and symptoms of nausea in animals whose stomachs had been completely removed. They conclude, therefore, that the emetic action is due in great part, if not entirely, to action on the vomiting centre.

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[3] Jour. Amer. Med. Assn., 1914, lxiii, 1746; Dental Cosmos, 1914, lvi, 948.

[4] Arch. Internat. de Pharmacod., 1902, xi, 9.

[5] Arch. f. exper. Path. u. Pharmakol., 1879, xi, 231.

[6] Jour. de Pharmacie, 1817, iii (quoted by Podwyssotzki).

[7] St. Bartholomew's Hosp. Reports, 1869, v, 1218; and 1871, vii, 91.

The changes induced in the intestinal tract, which come in from 18 to 24 hours after administration of emetin, may be summarized as follows: The mucosa of the small intestine and, to a less extent, that of the large intestine may be only slightly injected, with a catarrhal swelling, or the whole surface may be of a dark red color, and covered with a dry mucopurulent secretion. Sometimes the general reddening is absent and there are seen hyperemic areas covered with a yellowish exudation. Numerous sharp walled round ulcers are occasionly seen.

On the circulation, the paralyzing effect of emetin on the heart muscle, described by Duckworth, has been confirmed by later workers. Podwyssotzki[10] has shown in the frog's heart that an irregularity of rhythm develops early, both auricle and ventricle beating more slowly, but the ventricular slowing being more marked than the auricular. The auricle may contract twice to a single ventricular contraction, but soon the difference becomes greater, and the auricle may have many contractions to one of the ventricle. Eventually both auricle and ventricle stop in diastole, and are no longer able to respond to stimulation. In mammals, moderate doses caused a sharp fall in blood-pressure, with a quick recovery. With fatal doses the blood-pressure sinks to zero in a few seconds with an accompanying stoppage of the heart.

The action on the central nervous system has also been carefully examined by Podwyssotzki. In the frog, there is a general paralysis coming on in from ½ to 1½ hours. This begins with a depression of voluntary movements, with no changes in reflex activity. Later the reflexes disappear, while the voluntary muscle and motor nerves remain unaffected. According to this work, therefore, the drug produces a slowly descending central paralysis. Podwyssotzki was unable to detect a toxic effect on either voluntary muscle or motor nerve, although Kobert[11] later found that if the dose be large, a definite impairment of muscular function occurs.

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[8] Phila. Med. Times, 1878, viii, 554.

[9] Jour. Pharmacol. and Exper. Therap., 1915, vii, 233.

[10] Loc. cit.

The action on the respiratory tract is one of especial interest, since ipecac has been so largely used as an expectorant and also to check pulmonary hemorrhage. Magendie and Pelletier found in animals killed by emetin an inflammatory condition of the lungs. Duckworth found the lungs hemorrhagic and edematous, and the bronchi strongly injected. Podwyssotzki also found edema and marked irritation, but not in all of his experiments, and states that the pulmonary action is not a constant one. In a study on a series of patients with pulmonary disease given emetin, Zepf[12] was unable to observe any increase in amount or fluidity of bronchial expectoration. In two of the cases hemoptysis developed. This latter result together with the liability to cause vomiting brought Zepf to the conclusion that emetin is actually contra-indicated in pulmonary hemorrhage.

Of other organs acted on, the kidney undergoes some damage according to Foulkrod, who found albuminuria in animals given emetin. Zepf also found small amounts of albumin in most of the cases referred to above. No account is given of changes in the liver except a statement by Foulkrod that the sugar content is less than normal.

The changes in metabolism under emetin, have been studied by Meyer and Williams.[13] They found that emetin brings about a decrease in the carbon dioxide content of the blood, the oxygen content remaining unchanged. This effect, which is considered as one due to acidosis, they believe to result from an inhibition of cellular oxidation processes.

There remains the question of excretion of emetin. Some of the earlier experimenters state that the drug can be detected in the stomach after subcutaneous injection. Foulkrod states that it is excreted unchanged in part through the kidney, in part through the mucous membrane of the stomach and intestine. The methods used, however, are such as to invalidate these findings. Podwyssotzki and also Lowin were unable to detect the drug in any of the excretions.

In our own experiments, we have first noted the cause of death in emetin poisoning.[14] There are three types of this, dependent on the dose and manner of administration. Death occurs most promptly following intravenous administration and is due to cardiac paralysis. If a sufficiently large dose be given by subcutaneous injection (in cats 0.15 gm. per kilogram weight) death occurs usually in about 4 hours, and is due to respiratory failure. The heart is also affected and this is a contributory factor. With smaller doses death occurs in from 18 to 36 hours, and is due primarily to gastro-intestinal changes.

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[11] Therap. Monatsh., 1902, xvi, 387.

[12] Arch. internat. de Pharmacod., 1904, xii, 345.

[13] Arch. f. exper. Path. u. Pharmakol., 1881, xiii, 70.

[14] The emetin used in these experiments was obtained from Hoffmann-La Roche Chemical Works, Inc., who guaranteed its purity.

It is only in the last type of poisoning, that is, where death does not occur until after 18 hours, that definite postmortem changes are found.

With large doses of emetin, the chief site of lesion is the gastro-intestinal tract. The mucosa is highly injected and hemorrhagic, and is covered with bile-stained secretion. There may also be seen small areas of ulcerations This condition is evident along the entire gastro-intestinal tract.

It is only with large doses that changes other than congestion may be seen in the liver and these consist only of a few scattered areas of focal necrosis. The lungs usually appear emphysematous and anemic with a slight amount of edema. The bronchi are hyperemic. The heart, kidneys, and other organs show evidences of congestion only.

If smaller doses are given so that the animal may survive for 3 or 4 days, the reactions are not so marked and have a tendency for selective location. In these cases the mucosa of the stomach is rarely affected. The duodenum and the upper part of the jejunum show the characteristic changes, which diminish in intensity downward, the lower part of the small intestine often appearing normal. The cecum and large intestine take on the hemorrhagic appearance that is seen in the upper part of the tract.

From the changes induced in the gastro-intestinal tract, it is safe to assume even in the absence of chemical tests, that emetin is excreted in greatest amounts by the stomach and intestines. It would seem also that the excretion is chiefly through the upper part of the small intestine, since with smaller doses this is the part most strongly affected. In respect to this excretion, emetin may be classed with colchicin, diphtheria toxin, the heavy metals and many other drugs[15] which produce similar gastro-intestinal changes.

In studying the effects of emetin on the circulation we determined first those which were shown by blood-pressure variations. In a medium sized anesthetized dog, the intravenous injection of 0.01 gm. of emetin hydrochloride causes a very temporary and hardly noticeable rise in blood-pressure which is followed by a sharp fall. The pressure then rather quickly rises to the normal level or to a point slightly above normal. The fall in pressure, which is the characteristic change, averages about 40 mm. Hg. when the initial pressure is about 150 mm. Hg., that is, the fall is approximately 25 per cent. The whole cycle of change takes place in from 2 to 2½ minutes as a rule (Fig. 1). Some exceptions to these statements may be noted in that the fall in pressure may not be as marked, the recovery less rapid, and the subsequent rise above normal more prolonged.

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[15] Heubner, Arch. f. exper. Path. u. Pharmakol., 1907, lvi, 370.

With larger doses, up to 0.04 gm., the blood-pressure changes are similar but the fall is more marked. It is not, however, definitely proportional to the dose. After the initial injection subsequent ones of the same amount produce successively increasing effects, that is, both the actual and percental fall becomes greater. In some instances after 0.04 gm., and as a rule after doses above this, recovery fails to occur after the drop in pressure. The pressure continues to fall gradually until the zero line is reached when death occurs. With the low pressure the heart rate is markedly decreased.

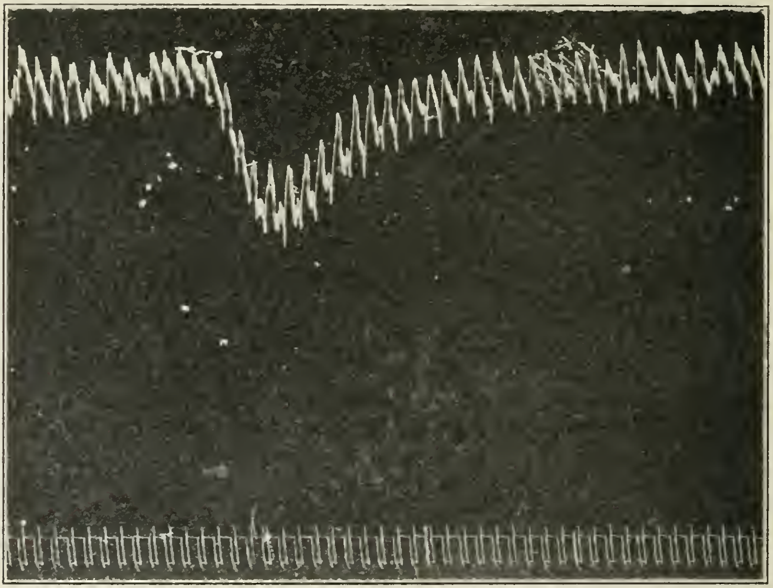

FIG. 1.—Carotid blood-pressure in a dog, showing the fall and recovery following an intravenous injection of 10 mgs. emetin hydrochloride.

Volumetric changes in different organs have been studied in relationship to the blood-pressure changes described. The volume of the kidney, loop of intestine, and the leg decreases simultaneously with the fall in pressure (Fig. 2). It follows, therefore, that the fall in blood-pressure is not due to a dilatation of bloodvessels, but must be ascribed entirely to a cardiac weakness. This is what the earlier workers on emetin have assumed.

In studying more directly the effect of the drug on the heart we have confirmed the results obtained by Podwyssotzki and Lowin in the frog's heart. The application of a few drops of a 1 per cent. emetin solution to an exposed frog's heart induces a typical picture of heart block. There is first noted a progressive slowing in the rate of contraction of both auricle and ventricle. Later an occasional dropping out of a ventricular beat occurs, and then a complete dissociation, the auricular-ventricular rhythm being 2 to 1, then 3 to 1, 5 to 1, etc. Finally the ventricle contractions stop, the

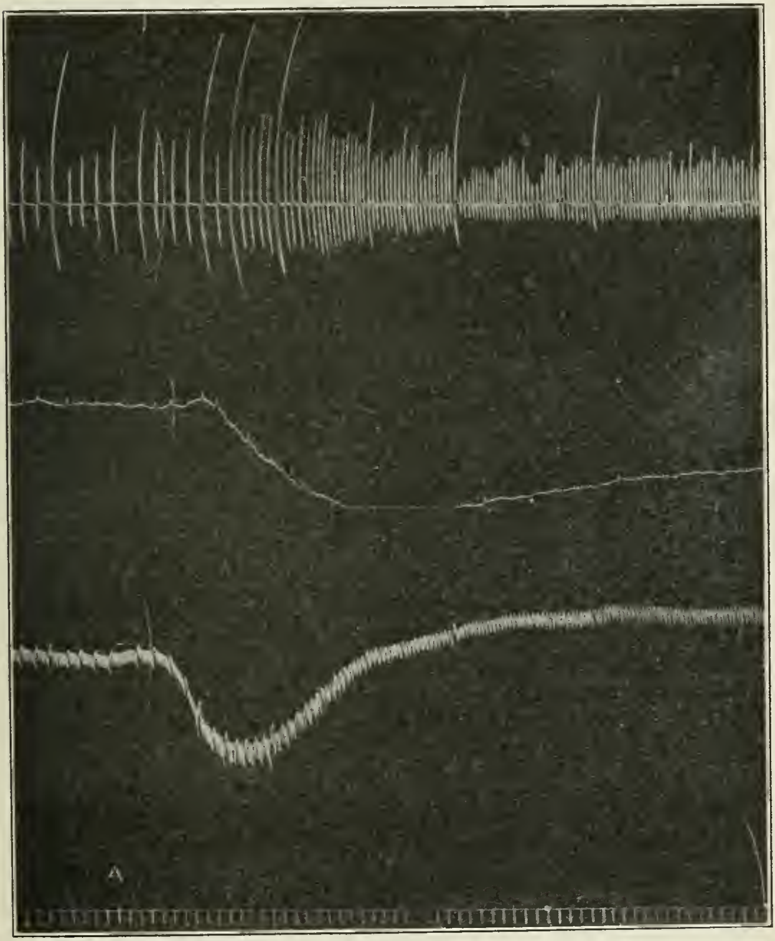

Fig. 2.—Record of respiratory movements (upper), intestinal volume (middle), and carotid blood-pressure (lower) in dog. Time marker registers three second intervals. At *A*, 20 mgs. emetin hydrochloride was injected intravenously. Coincident with the fall in pressure the intestinal volume lessens while the respiratory movements become increased.

auricle beating for a considerable time longer. The turtle's heart behaves in a similar manner (Fig. 3).

The record of the contractions of the mammalian heart, taken with a Cushny myocardiograph, fails to show a dissociation of auricle and ventricle. In the dog, following an intravenous injection of 0.04 gm., the auricle shows a marked weakening in contraction, the ventricle a lessened contraction and an increased relaxation as well (Fig. 4). These changes occur synchronously with the fall in blood-pressure, and the decrease in volume of organs tested. With larger doses the effect is intensified, and the heart contractions cease. The auricular contractions stop some time before those of the ventricle.

The cardiac weakening and fall in blood-pressure are not influenced by either cutting the vagi or administration of atropin. The action, therefore, is on the heart muscle and not on the vagus. An improvement occurs after both epinephrin and strophanthin, but this is temporary, and delays only for a short time the complete cardiac paralysis. The myocardiographic tracing is identical with that obtained with chloroform or other cardiac depressants.[16]

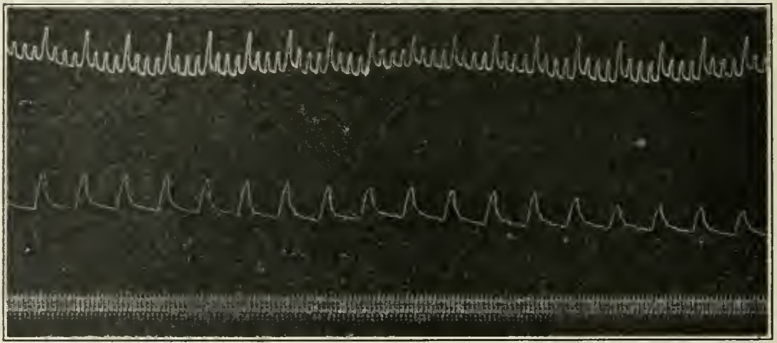

Fig. 3.—Record of contractions of turtle's heart perfused with Locke's solution, to which emetin hydrochloride has been added. The upper record shows auricular contractions, the lower, ventricular. Time marker registers one-second intervals. The auricular-ventricular rhythm is 4 to 1.

We have repeated and confirmed the work of others on the action on the central nervous system. In the frog the action is that of a slowly descending paralysis. At a time when this is complete, with abolition of all reflex activity, both motor nerve and muscle respond to stimulation in a normal manner. The injection of a dose of 0.005 gm. of emetin into the dorsal lymph sac, which is sufficient to produce these effects, brings on a cardiac paralysis in the frog which becomes complete before the central nervous paralysis.

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[16] We have noted a fact here worth calling attention to. In one experiment, in which the heart was still in fairly good condition, the injection of epinephrin produced a sudden complete paralysis. We have seen a similar effect in a heart weakened by chloral. Epinephrin, in other words, by causing a great rise in blood pressure may overwhelm a weakened heart.

In mammals, cats and dogs, there is evidence of some cerebral depression as is shown by the greater quiet of the animal. The doses which induce this, however, cause nausea or vomiting, and the depression may be looked on as an accompaniment of these

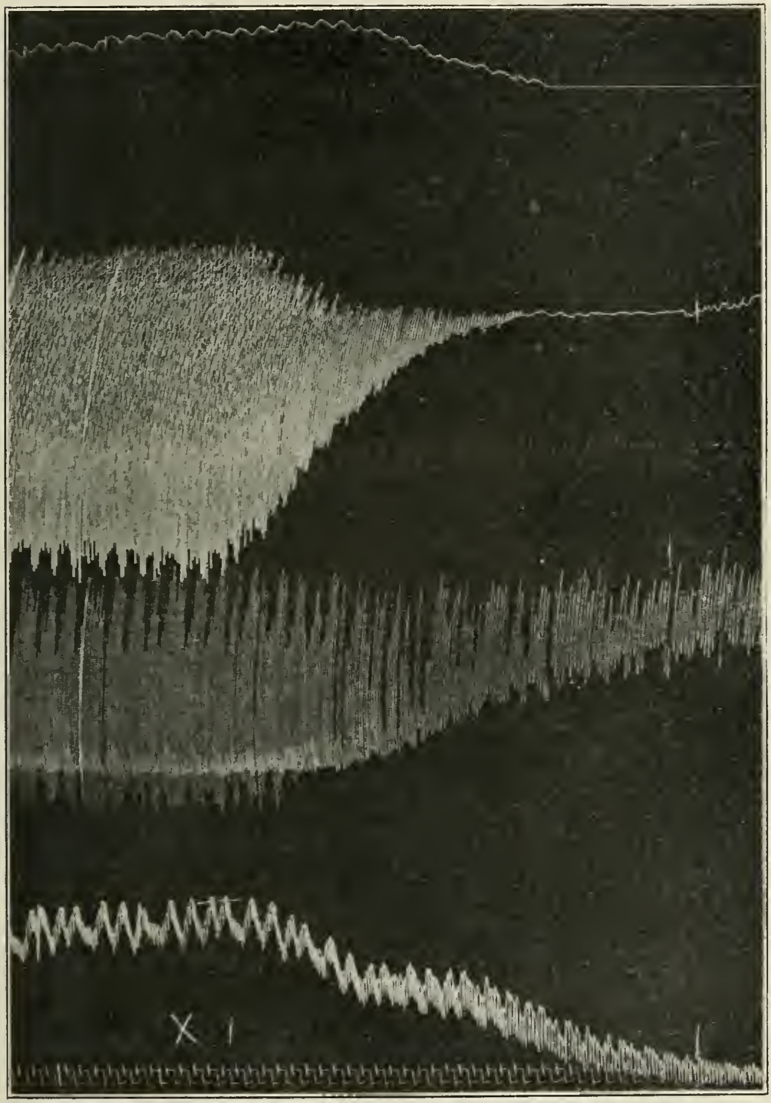

FIG. 4.—Record of kidney volume, auricular contractions, ventricular contractions, and carotid blood-pressure in dog. In the cardiac tracing the upstroke is diastolic, the down stroke systolic. At *X*, 40 mgs. emetin hydrochloride injected intravenously.

effects. Only with doses which approach lethal ones, does the depression become marked and out of proportion to the emetic effect.

In connection with the action on the central nervous system the effect on respiration is of interest. According to Kunkel[17] the respiration is effected before cardiac weakness develops, and respiratory stoppage occurs before cardiac paralysis. This statement should be modified somewhat. With subcutaneous injections respiration stops before the heart. The latter shows depression early, however, and when the respirations stop the blood-pressure is very considerably lowered and the heart contractions weakened. Artificial respiration at this stage fails to bring about a circulatory recovery, although the circulation may continue, at a low level, for a considerable time. With intravenous injections, coincident with the fall in blood-pressure, the respiratory movements increase in rate or volume (Fig. 2) and continue for some time after the heart has stopped beating and the blood-pressure fallen to zero. The respiratory changes in this instance may be considered as dependent on circulatory failure.

In short experiments emetin has little influence on the kidney as far as diuresis is concerned. During the fall in blood-pressure a diminution or stoppage in urine flow occurs, as would naturally be expected. Otherwise no changes are noticed. In dogs given daily injections of emetin the amount of urine passed increases on each succeeding day and may finally reach two or three times the normal output. The urine contains small quantities of albumin, but gives no evidence of severe damage to the kidney. The effect on urine output is such as may occur from any mild irritation, and postmortem examination of the kidney shows that this is the only morphological change usually seen.

A few experiments have been made on the uterus. The uteri of virgin guinea-pigs and of those in early pregnancy were used, being suspended in an oxygenated Locke solution, according to the method of Dale.[18] On adding emetin to the fluid no change in uterine movement was obtained excepting a slight increase in tonicity, as evidenced by a shortening of the muscle. The effect is quite distinct from that obtained by adding such drugs as ergot or pituitary extract.

The only study of metabolism in animals given emetin is that made by Meyer and Williams. We have carried this work further in so far as nitrogen metabolism is concerned. The experiments were carried out on fasting dogs, and the urine collected in 24-hour periods. The total nitrogen was estimated by the Kjehldal method, the urea and ammonia by the Van Slyke and Folin methods respectively. There is seen an increase in the total nitrogen, urea nitrogen, and ammonia nitrogen following the emetin administration (see Table). This increase in nitrogenous metabolism is in accord with the results of Meyer and Williams. Similar changes are induced by arsenic, phosphorous, potassium cyanide, and other poisons and are commonly explained as results of interference with intracellular metabolism with an accompanying acidosis.

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[17] Handbuch der Toxikol., 1901, p. 843.

[18] Dale and Laidlaw, Jour. Pharmacol. and Exper. Therap., 1912, iv, 75.

DOG No. XVI.

Day.	Urine in 24 hrs. C.c.	Sp. Gr.	Total "N." Gm.	Urea "N." Gm.	NH_3 "N." Gm.
Oct. 27	120	1.040	3.59	2.42	0.210
Oct. 28	70	1.062	3.36	1.17	0.140
Oct. 29	59	1.060	2.89	1.94	0.165
11.30 A.M. Injected 2.5 c.c. emetin (1 per cent. solution).					
Oct. 30	80	1.070	3.87	2.82	0.222
10.15 A.M. Injected 2.5 c.c. emetin.					
Oct. 31	120	1.065	5.25	4.30	0.319
Nov. 1	155	1.052	5.05	4.24	0.293
Nov. 2	150	1.034	3.95	3.65	0.277
11.00 A.M. Injected 2.5 c.c. emetin.					
Nov. 3	315	1.030	5.64	3.21	0.389

DOG No. XVII.

Nov. 9	60	1 060	3.06	2.37	0.217
Nov. 10	65	1.050	3.30	2.71	0.143
Nov. 11	65	1.050	3.43	2.68	0.448
Nov. 12	65	1.050	3.05	2.69	0.126
Nov. 13	75	1.060	3.28	2.87	0.105
Injected 3 c.c. emetin (1 per cent. solution).					
Nov. 14	100	1.070	4.70	4.42	0.140
Injected 3 c.c. emetin solution.					
Nov. 15	175	..	6.16	5.49	0.299

Finally in an attempt to explain the former wide-spread use of emetin in checking hemorrhage, we have determined, by means of Wright's coagulometer, whether the coagulability of the blood is influenced by the drug. The subcutaneous injection of a good sized dose of emetin into a cat fails to affect the coagulation time to any appreciable degree. Since then there is no action on the lungs, blood, bloodvessels, or uterus, which would account for a hemostatic effect, we are forced to assume that such an effect, if present, is due to the general relaxation which is an accompaniment to the action of emetics given in too small doses to induce vomiting. As a matter of fact we have noticed a fluidity of the blood on autopsy.

We have not attempted to study the action of emetin on the ameba. Its specificity in this connection seems no longer open to question. Vedder[19] had shown, conclusively, that emetin is strongly amebacidal to all forms of non-pathogenic ameba in the dilution of 1 to 100,000. Rogers[20] demonstrated that an equal toxicity is shown against pathogenic forms. Weaker solutions while not so strongly amebacidal, exercise a definitely deleterious action on the parasite. To obtain a 1 to 100,000 solution in the blood it would be necessary to have about 0.05 gm. of emetin in the circulation at one time. As the dose given is generally smaller than this, and it is not completely taken up into the blood stream from the point of injection for some hours, it is evident that the dilution is considerably greater than this figure. It seems safe to assume, however, that emetin is excreted along the whole alimentary tract. In this case its longer stay in the excretory tissues, or the greater concentration in which it may exist during excretion, would account for a sufficiently strong amebacidal action.

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[19] Vedder, Bull. Manila Med. Soc., 1911, iii, 48; Jour. Am. Med. Assn., 1914, lxii, 501.

[20] Rogers, loc. cit.

Contrary to the statement of Lowin we have found, on patients, that emetin usually produces a definite local irritation after a subcutaneous or intramuscular injection. There is some redness, pain, swelling and occasionally edema in the part, most marked for the first two or three days, and gradually subsiding in about a week. If applied to mucous membranes there appear small pin-head-sized vesicles which rupture, leaving small ulcers. These, however, rapidly disappear. These effects are undoubtedly well known to all who have been using emetin in the treatment of pyorrhea alveolaris.

Summary. From our experiments we wish to emphasize the following points:

1. Emetin depresses and may eventually paralyze the heart.
2. It is a powerful gastro-intestinal irritant whether given by mouth or subcutaneous injection.
3. It causes a definite derangement of metabolism, characterized by an increase in nitrogen loss and an acidosis.
4. While in normal individuals given moderate doses, these actions may not be of importance, in pathological states of the circulation, intestinal tract, or metabolism, they may be a very definite source of danger.

EFFECTS OF RETENTION IN THE KIDNEY OF MEDIA EMPLOYED IN PYELOGRAPHY.

By William F. Braasch, M.D.,

and

Frank G. Mann, M.D.,

MAYO CLINIC, ROCHESTER, MINNESOTA.

With the recognition of the diagnostic value of pyelography came the realization that the method was not without danger to the patient. Deaths were reported by various observers, which were evidently the direct result of pyelography. Animal experimentation demonstrated that death might follow the introduction of colloidal silver solution into the renal pelvis with overdistention. The introduction of the medium by means of gravity so as to obviate the danger of overdistention reduced the possibility of renal injury to a great degree.

In 1913 one of us[1] reported several cases of hydronephrosis removed at operation in which necrosis of the renal cortex was evident, although the pelvis had not been overdistended. It was believed that secondary retention of colloidal silver in the renal pelvis without overdistention could cause necrosis in the renal parenchyma. This observation was later corroborated by Krotoszyner[2] and by Keyes and Mohan,[3] who reported similar clinical observations. Keyes and Mohan further demonstrated the process conclusively by injecting a small amount of colloidal silver into the renal pelvis of dogs and then ligating the ureter. The kidneys removed later showed numerous areas of cortical necrosis as the result of the retention of the colloidal silver. From a histological study of the areas of resulting necrosis it was evident that the minute particles of metallic silver deposited in the parenchyma were the underlying cause of the necrosis.

The avenues of introduction of the metallic deposits have not been definitely determined. It has been argued that the silver deposits found in the tubules reached the glomeruli primarily by means of lymphatic and vascular absorption, and were later secreted into the tubules. The histological evidence advanced in support of this theory is hardly conclusive. It would seem logical to hold that when the natural drainage of the renal pelvis is occluded, peristaltic contraction may force the pelvic contents into the tubules. Microscopic examination of any of the different solutions of colloidal silver employed in pyelography will show the presence of undissolved particles of metallic silver; a perfect solution is hardly possible, a fine suspension being the medium employed. The silver deposited in the renal substance acts like any other foreign body in that it causes suppuration and necrosis of the adjacent tissue. With multiple deposits of metallic silver with adjacent foci of infection the resulting condition is practically that of an acute septic nephritis. As might be expected, clinical symptoms and resulting fatality are identical with acute septic nephritis. Necessarily, the indications for surgical treatment are similar in both conditions. Nephrectomy is indicated if the patient has a persistent high temperature and evidence of severe intoxication, which usually marks this condition following pyelography. That such a complication will occur in a comparatively small percentage of cases of hydronephrosis following pyelography made with proper technical precaution is evidenced by the fact that in more than 5000 cases at the Mayo Clinic in which pyelography was employed, marked focal necrosis was found in but eight cases. In all of these the kidney was found to be actively secreting, although the drainage was temporarily interfered with. Less reaction followed when the substance of the kidney was largely destroyed. No deaths occurred which could be attributed directly to pyelography. However, the element of danger which is present in spite of every precaution would necessarily restrict its employment.

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[1] Braasch, W. F.: Recent Progress in Ureteropyelography. Jour. Michigan Med. Soc., 1913, xii, 189–190.

[2] Krotoszyner: Untoward Results of Pyelography. Surg., Gynec. and Obst., 1914, xix, 522–527.

[3] Keyes, E. L., and Mohan, H.: The Damage Done by Pyelography. AM. JOUR. MED. SC., 1915, cxlix, 30–41.

To prevent pyelography from falling into disuse as a method of diagnosis because of the possible danger involved in its employment, various forms of silver have been tried. Among the different media suggested, silver iodide in emulsion[4] and silver iodide in suspension[5] have been found less harmful in their effect. Although the frequency of focal necrosis was thus unquestionably diminished, nevertheless it was not entirely eliminated. Two severe cases of focal necrosis following the retention of silver iodide injected into a hydronephrosis came under our observation. Moreover, the silver iodide suspension causes considerable local irritation. The injection of so viscid a substance as silver iodide emulsion with a syringe is objectionable because of the difficulty of gauging the degree of pressure in its introduction and the amount necessary for pelvic distention. The latest medium suggested, namely, thorium,[6] evidently obviate many of the objections to those previously used, and has the following advantages: (1) it is in actual solution and not suspension; (2) it does not cause local irritation; (3) it can be introduced by means of gravity.

Thorium nitrate solution offers the safest medium for pyelography. Unfortunately, it casts a less distinct shadow than the colloidal silver preparations in common use. Further, it does not bring out the details of the calyces nor of the ureter as well as the silver preparation. It is peculiar that solutions of greater concentration (20 per cent.) cast no denser shadow than a lesser (10 or 15 per cent.).

That focal necrosis may occasionally occur following the use of thorium was evident in a case of hydronephrosis which recently came under our observation. Microscopic examination of the tissue of the kidney removed showed numerous areas of round-celled infiltration such as are usually the result of infection. No evidence of metallic deposit was visible. The infection was predominant in the tissues, about the tubules and but few glomeruli were involved.

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[4] Kelly, H. A., and Lewis, R. M.: Silver Iodide Emulsion—a New Medium for Skiagraphy of the Urinary Tract. Surg., Gynec. and Obst., 1913, xvi, 707–708.

[5] Young, E. L.: A New Preparation for Pyelography. Boston Med. and Surg. Jour., 1915, clxxii, 539–544.

[6] Burns, J. E.: Thorium, a New Agent for Pyelography. Preliminary Report. Jour. Am. Med. Assn., 1915, lxiv, 2126–2127.

Prior to the use of pyelography the diagnosis of renal urinary retention was usually arrived at by means of the ureteral catheter and the overdistention method. Following simple ureteral catheterization we have observed the presence of a considerable degree of focal suppuration in several kidneys subsequently removed at operation. Microscopic examination of these areas showed that they were of bacterial origin. It is quite impossible to introduce either a ureteral catheter or bland fluid into the renal pelvis which has insufficient drainage without danger of subsequent infection. However, the exercise of every precaution to keep such a catheter and the medium introduced sterile will somewhat reduce the number of cases of infection, but will not exclude them. We are under the impression that the focal necrosis and areas of suppuration noted in the case with thorium retention were the result of coincident bacterial infection. The use of opaque media, as in pyelography, should not bear the entire blame for cortical necrosis. Moreover, the kidney in which focal necrosis results following retention is primarily a "surgical kidney," and its sacrifice will not usually alter the necessary procedure. As a matter of precaution it is advisable always to ascertain whether the other kidney is functionating properly before either catheterization, fluid overdistention, or pyelography is attempted in a case in which pelvic retention is suspected.

The object of the following series of experiments which were begun in April, 1914, was to study the comparative effect of retention in the kidney of the various media used in pyelography and to determine whether the retention of chemical irritants in the pelvis of the kidney would produce lesions of that organ. This was accomplished by either a complete or partial occlusion of the ureter of a dog after injecting the substance into the pelvis of the kidney. The routine technic was to expose the ureter, usually the right, through a lumbar incision and carefully dissect it free for a short distance, about two inches, from the kidney. When the occlusion was made complete the free portion of the ureter was ligated and the solution injected through it into the pelvis. The ureter was again ligated proximal to the entrance of the needle and sectioned between the ligatures. When a partial occlusion only was made the ligature was tightened over the needle at the point where it entered the lumen of the ureter. As the results did not materially differ, all the experiments will be reported together.

The capacity of the dog's kidney varies, but is practically always greater than 1.5 c.c. In order to avoid immediate distention of the pelvis, only 1 c.c. was used. After injecting and ligating the ureter it was replaced and the wound carefully closed. The specimens were obtained at various times after injection, but were approximately the same for the different substances used.

The effects of retention of the following substances were studied experimentally: (1) 1 per cent. solution sodium chloride; (2) saturated solution of boracic acid; (3) saturated solution of sodium citrate; (4) methylene blue; (5) 5 per cent. collargol; (6) 25 per cent. collargol; (7) 25 per cent. argyrol; (8) 25 per cent. cargentos; (9) washed staphylococci; (10) emulsion of silver iodide; (11) silver iodide in quince-seed emulsion; (12) 15 per cent. thorium nitrate neutralized; (13) 20 per cent. solution of thorium nitrate as used clinically; (14) 20 per cent. solution of thorium nitrate unneutralized. In many of these experiments the uninjected kidney was also studied.

In studying the kidney it was necessary to differentiate three distinct conditions: (1) the effect of the hydronephrosis; (2) the effect of the infection; (3) the effect of the retained substances. The effect of the hydronephrosis on the substance of the kidney could easily be distinguished. However, it was not always possible to determine whether the condition found in the kidney was due to an infection, to the retained substance, or to both.

Grossly, the kidney usually presented a degree of hydronephrosis depending on the length of time after ligation. The fluid which escaped from the pelvis was quite often very turbid, and it was often possible to find some of the injected solution. In a few cases there was a necrosis of the ureter at the point of ligation, with the formation of a perinephritic cyst.

The capsule was usually thickened. On section the renal substance was thin and firm. Quite often it was not possible to demonstrate grossly any changes in the substance of the kidney due to the injected solution. However, in some instances there were pin-point hemorrhagic areas or small abscesses. These were usually in the cortex near the surface. In two instances the medulla was stained throughout with the injected substance. The pelvic mucosa practically always showed changes. These consisted of hemorrhagic spots or areas of necrosis. The mucosa was usually stained with injected solution, and some of the substance could be scraped from the surface. The result of the microscopic study is as follows:

No.	Solution.	Time.	Change.
1	Methylene blue	10 days	None.
2	" "	26 "	Slight. A few areas show infiltration.
3	" "	15 "	None.
4	" "	22 "	None.
5	" "	12 "	Moderate. Several areas of focal inflammation. Infection?
6	5 per cent. collargol	15 "	Marked. Entire medulla infiltrated; areas of necrosis; several cortical areas of pigmentation.

No.	Solution.	Time.	Change.
7	5 per cent. collargol	9 days	Moderate. Several areas of infiltration of deeply staining cells.
8	“ “ “	25 “	Marked. Many areas of pigmentation definitely organized throughout the remaining renal substance.
9	“ “ “	15 “	Slight. A few areas of infiltration.
10	“ “ “	8 “	Moderate. Several areas of necrosis.
11	“ “ “	7 “	None.
12	“ “ “	14 “	Slight. Several areas of infiltration of deeply pigmented cells in the cortex.
13	25 per cent. collargol	25 “	Marked. Entire remaining renal substance infiltrated. Few normal cells left. Many areas of necrosis.
14	“ “ “	30 min.	Very slight.
15	“ “ “	7 days	Slight. Many cells of the collecting tubules pigmented.
16	20 per cent. collargol	7 “	Slight infiltration of the pelvic mucosa.
17	25 per cent. collargol	4 “	None.
18	25 per cent. argyrol	22 “	Marked. Infiltration of all the remaining renal substance.
19	“ “ “	5 “	None.
20	“ “ “	24 “	Moderate. Marked infiltration with several areas of necrosis.
21	“ “ “	15 “	Slight. A few areas of pigmentation.
22	“ “ “	8 “	Very slight.
23	“ “ “	7 “	None.
24	25 per cent. cargentos	30 “	Marked. Many areas of pigmentation scattered throughout the remaining renal substances.
25	“ “ “	13 “	Moderate. Many areas of pigmentation found mainly in the medulla.
26	“ “ “	30 “	Marked. Remaining renal substance infiltrated. Many areas of necrosis.
27	“ “ “	5 “	Slight. Several collecting tubules contain the brown-colored substance. Pelvic mucosa is infiltrated.
28	“ “ “	7 “	Slight. A very few areas infiltrated with deeply staining cells.
29	“ “ “	7 “	None.
30	Silver iodide	24 “	None.
31	“ “	15 “	None.
32	“ “	16 “	Moderate. Marked infiltration.
33	“ “	7 “	None.
34	“ “	12 “	Very slight.
35	Emulsion silver iodide with quince seed	7 “	Very slight.
36	Emulsion silver iodide with quince seed	7 “	Very slight.
37	Emulsion silver iodide with quince seed	9 “	None.
38	Emulsion silver iodide with quince seed	58 “	No renal structure left.
39	Emulsion silver iodide with quince seed	9 “	None.
40	Washed staphylococci	3 “	Slight. A few abscesses.
41	“ “	2 “	Marked. Many abscesses.
42	“ “	5 “	Moderate. A few abscesses.
43	15 per cent. thorium nitrate	4 “	None.
44	15 per cent. thorium nitrate	9 “	None.
45	15 per cent. thorium nitrate	14 “	None.

No.	Solution.	Time.	Change.
46	15 per cent. thorium nitrate	6 days	None.
47	15 per cent. thorium nitrate	10 “	Slight?
48	1 per cent. NaCl	4 “	None.
49	“ “	10 “	None.
50	Saturated solution, boracic acid	10 “	None.
51	Saturated solution, boracic acid	6 “	None.
52	20 per cent. solution thorium nitrate	10 “	Microscopic picture: Acute infection. Renal substance filtrated throughout, complete loss of normal structure in many areas. Definite abscesses in some areas.
53	20 per cent. solution thorium nitrate	6 “	Marked. Substance of kidney infiltrated throughout. Definite abscesses in some areas. Tubule mostly disappeared or badly damaged. Glomeruli seem less affected than tubules.
54	20 per cent. solution thorium nitrate	7 “	None.
55	20 per cent. solution thorium nitrate	4 “	Slight.
56	Saturated solution citrate	7 “	A few small subcortical infiltrations which appear to be beginning abscesses.
57	Saturated solution citrate	4 “	None.
58	20 per cent. solution thorium nitrate	3 “	None.
59	20 per cent. solution thorium nitrate	3 “	None.
60	Saturated solution citrate	3 “	Slight. There are a few areas of beginning infiltration.
61	20 per cent. solution thorium nitrate	3 “	Slight. There are a few areas of beginning infiltration.
62	20 per cent. solution thorium nitrate	7 “	None.
63	20 per cent. solution thorium nitrate	7 “	Slight. There are a few beginning areas of infiltration.
64	20 per cent. solution thorium nitrate	3 “	Moderate. There are a few very large areas of infiltration in the cortex.
65	Saturated solution citrate	7 “	None.
66	20 per cent. solution thorium nitrate (unneutralized)	2 “	Moderate. There are some cortical areas of infiltration.
67	20 per cent. solution thorium nitrate (unneutralized)	2 “	Moderate. There are a few areas of beginning infiltration.

An attempt was made to estimate the changes due to the injected solution. These changes varied, but in general they consisted of areas of focal necrosis with or without actual demonstration of the localized substance. These areas were usually located in the cortex but have been found in the medulla. The lesion appears to consist of an accumulation of the substance in the tubules of the kidney. We have not definitely determined whether the sub-

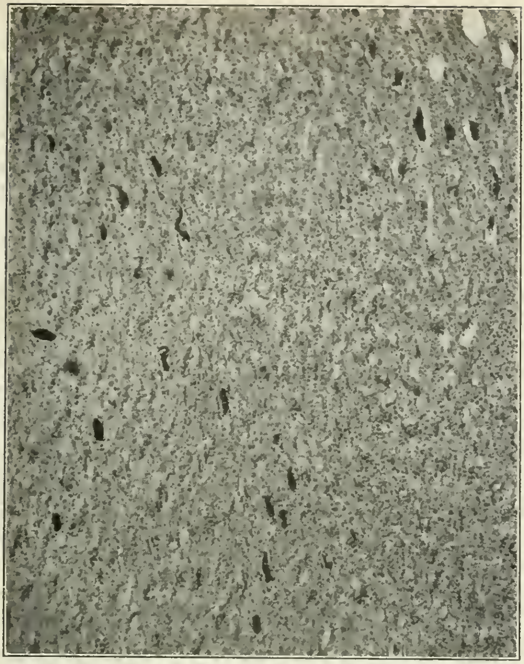

Fig. 1.—Experiment 27. Photomicrograph (× 50) showing cargentos in kidney tubules five days after injection.

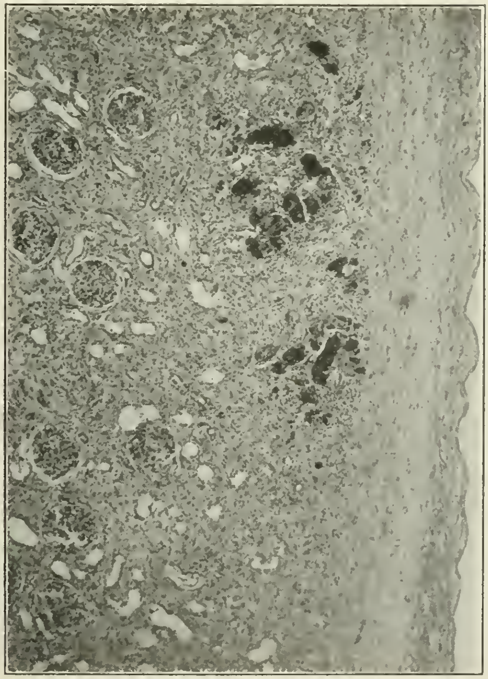

Fig. 2.—Experiment 6. Photomicrograph (× 60) showing collargol in the kidney tubules fifteen days after injection.

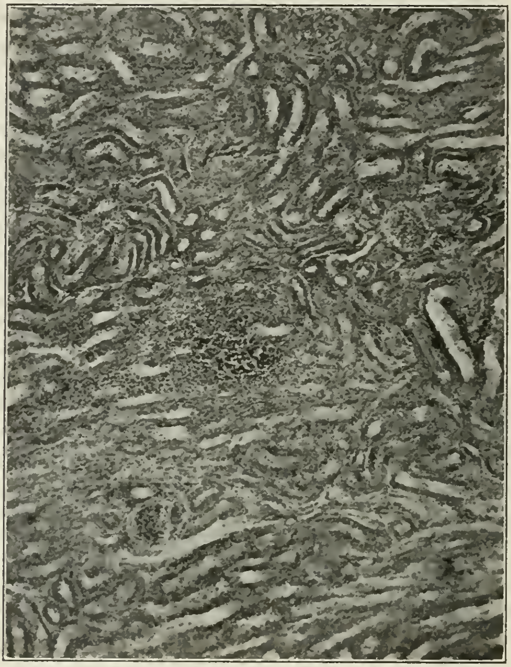

Fig. 3.—Experiment 25. Photomicrograph (× 60) showing a localized area of cargentos thirty days after injection.

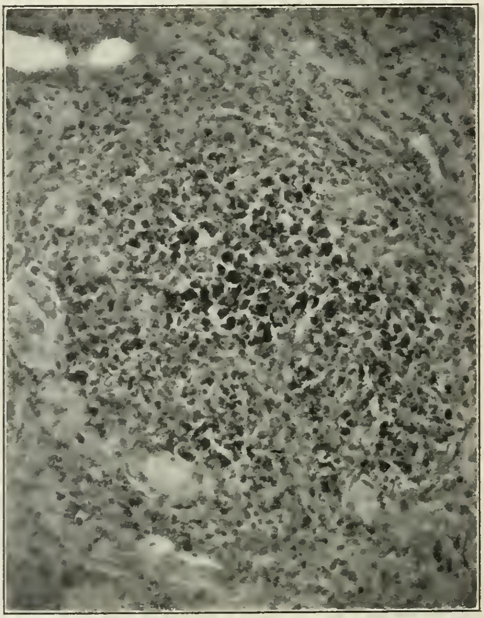

Fig. 4.—Experiment 8. Photomicrograph (× 200) showing a higher magnification of one of the areas in Fig. 3.

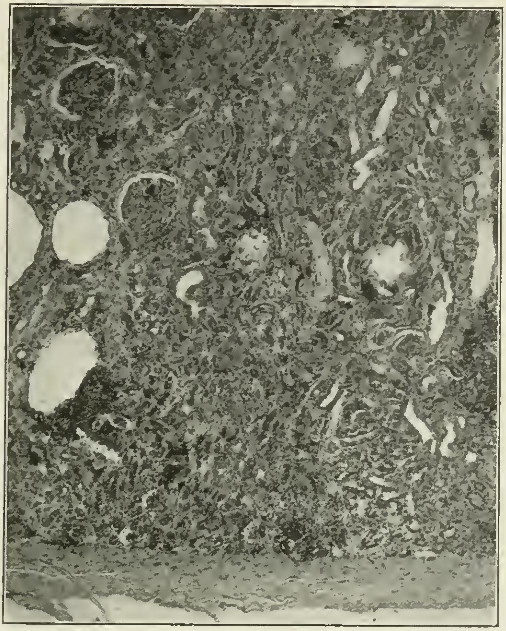

Fig. 5.—Experiment 47. Photomicrograph (× 50) showing some areas of infiltration in the periphery of cortex ten days after the injection of thorium nitrate.

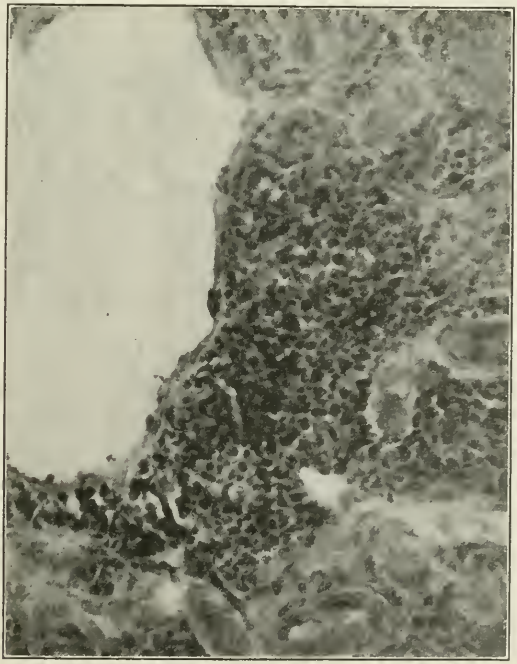

Fig. 6.—Experiment 47. Photomicrograph (× 225) showing higher magnification of one of the areas in Fig. 5. It is impossible to tell what part the solution played in its formation. It appears to be primary infection.

stance reaches the cortex through the tubules or by way of the blood and lymphatic vessels. Observations tend to show that in some instances either route may be followed. In a few instances lesions of the uninjected kidney have proved that the substance was absorbed and excreted. The lesions which follow excretion of the substance are usually located in the medulla. These are characterized by infiltration of large deeply staining cells. When organization takes place there is first formed an area of necrosis and hemorrhages in the immediate vicinity of the substance. Later a definite wall of connective tissue forms with absorption of the necrotic material. In many instances infection followed the localization of the substance so that it was impossible to differentiate the condition from a primary infection.

Results. The results of these experiments are tabulated briefly as follows:

1. The injection of 1 per cent. solution of sodium chloride and a saturated solution of boracic acid in two experiments each did not produce a lesion of the kidney.

2. The injection of a saturated solution of sodium citrate in four experiments produced lesions in two instances. The cultures of tissue was negative for bacteria in both of these positive experiments, and in one only were a few micrococci found in the fluid of the pelvis.

3. In the five experiments in which methylene blue was injected only one kidney showed a slight lesion. This lesion may have been due to an infection.

4. In seven experiments 5 per cent. collargol was injected. Lesions of various degrees of severity occurred in six.

5. In the five experiments in which 25 per cent. collargol was injected, lesions were found in four.

6. The injection of 25 per cent. arygol in six experiments produced lesions in four.

7. The injection of 25 per cent. cargentos in six experiments produced lesions in four.

8. In five experiments in which silver iodide was injected, moderate lesions were noted in two.

9. In five experiments in which silver iodide with quince seed was injected, slight lesions were found in two.

10. In five experiments 15 per cent. thorium nitrate was injected. A slight lesion was noted in one kidney. In order to test this substance to a greater extent, in one experiment the pelvis of the kidney was overdistended with 5 c.c. of the solution and in another 2.5 c.c. were injected. The first specimen was examined after four days and the latter after fifteen days. In neither were any changes noted which could be attributed to the injected solution.

11. The injection of a 20 per cent. solution of thorium nitrate, neutralized as used clinically, in ten experiments, produced lesions

of various degrees of severity in five. In two of these the kidney was very badly damaged. It is suggestive that in these two experiments the solution was used immediately after it had been made. It is possible that an old solution is better than one just freshly prepared. In the other three experiments in which lesions occurred the cultures of tissue and smears of the pelvic fluid were negative for bacteria.

12. The injection of 20 per cent. solution of thorium nitrate, unneutralized, in two experiments, produced lesions, particularly of the pelvis, in both. Smears of the pelvic fluid were negative in both of these experiments and cultures of tissue showed a few staphylococci, possibly a contamination.

CONCLUSIONS DERIVED FROM CLINICAL DATA. 1. The greatest danger in the use of silver preparations is their retention in actively secreting kidneys.

2. With multiple foci of necrosis the condition should be regarded as a septic nephritis and immediate nephrectomy is indicated.

3. Focal necrosis as the result of infection may follow the introduction of a ureteral catheter or of bland fluids into a pelvis with insufficient drainage.

4. Silver iodide suspensions are less harmful than the colloidal silver preparations.

5. Thorium nitrate in 10 or 15 per cent. solutions causes the least reaction but casts a less distinct shadow.

CONCLUSIONS DERIVED FROM EXPERIMENTAL DATA. 1. Mild chemical irritants, as sodium chloride and boracic acid, when injected and retained in the pelvis of the kidney do not produce lesions of that organ.

2. The effect of methylene blue was practically negligible.

3. More stringent chemical irritants, as sodium citrate and 20 per cent. thorium nitrate, when tested in the same drastic manner, produce lesions of the kidney, which seem directly due to the chemical injected, and not to any concomitant or subsequent infection.

4. Argyrol, collargol, and cargentos were about equally responsible for producing the most marked changes noted. It was often possible to find areas in which the metal could be distinguished.

5. The weaker solutions of colloidal silver did not appear to be less harmful than a more concentrated solution.

6. The silver iodide preparations produced less changes in the kidney than the other silver solutions. Of the two preparations of silver iodide, the one in which it is suspended in quince-seed emulsion caused the least necrosis.

7. So far as we have been able to determine by the method employed, thorium nitrate (15 per cent. solution) did not produce changes in the kidney except possibly in one experiment. Care must be taken in its preparation that the solution is thoroughly neutralized.

THE TRANSPLANTATION OF THE THYROID GLAND IN DOGS.

By Charles Goodman, M.D., F.A.C.S.,
CLINICAL PROFESSOR OF SURGERY, NEW YORK UNIVERSITY.

(From the Physiological Surgical Research Laboratory, New York University.)

Highly organized tissue cannot as yet be permanently transplanted from one organism to that of another. So much may be gleaned from the mass of material presented during the past four years by the various experimental workers in transplantation.

There is much laboratory and clinical evidence, however, that the implantation of large fragments of bony tissue is practicable. Albee reported 253 cases of autografts of bone, a large percentage of which were successes, and he concluded that the bone graft is reliable when taken with its enveloping membranes and contacted with bone. McWilliams has also recently shown the importance of the periosteum in transplanting the larger grafts of bone. Some discussion has arisen, it is true, as to the fate of the bone transplant. Borth now agrees with Axhausen, Phemister, and Lewis that the compact bone of the graft is absorbed and that it is replaced by bone formed by the periosteum and endosteum of the graft. Lewis holds that compact bone dies in the graft because of its physical properties which do not permit rapid enough absorption of serum to maintain the life of the bone until the vascular circulation is reëstablished.

Mauclaire reported five successful results out of a number of failures. He believes that if the successes of Küttner and Lexer in the transplantation of articular fragments taken from the cadaver are multiplied that such transplantations will give much better results than the best of resections. Cohn and Mann reported from their fifteen experiments that isolated bone grafts did not act as foreign bodies, nor were they absorbed after sixty days, even showing a tendency to outgrowth. According to MacEwen, if small grafts of compact bone could be used the bone would live, but, as Lewis stated, this ideal condition is rarely, if ever, secured in bone transplantation.

Lexer reported that although Schoene has carried out successfully skin transplantation in animals of the same litter and the same sex, that he himself has never seen any successful homoplastic skin grafts in man even between close relatives.

Erlacher succeeded in the transplantation of muscles, for after ninety-nine days the electrical tests showed that the transplanted muscles reacted normally to stimulation. But his experiments in the free transplantation of nerves were failures, although restoration of the peripheral part of the nerve took place after section.

Von Hacker has recently implanted the central stump of the accessory nerve directly into the trapezius in a case of paralysis of that muscle as a result of injury to the accessory nerve. The result was excellent.

Stich stated, in 1913, that arteries and veins which have been autoplastically transplanted will retain their vitality and become an integral part of the system. The different layers are microscopically shown to be completely intact, but when transplanted to different animals, and more especially when transplanted to animals of different species, they show a replacement by the tissues of the body to which they were transplanted.

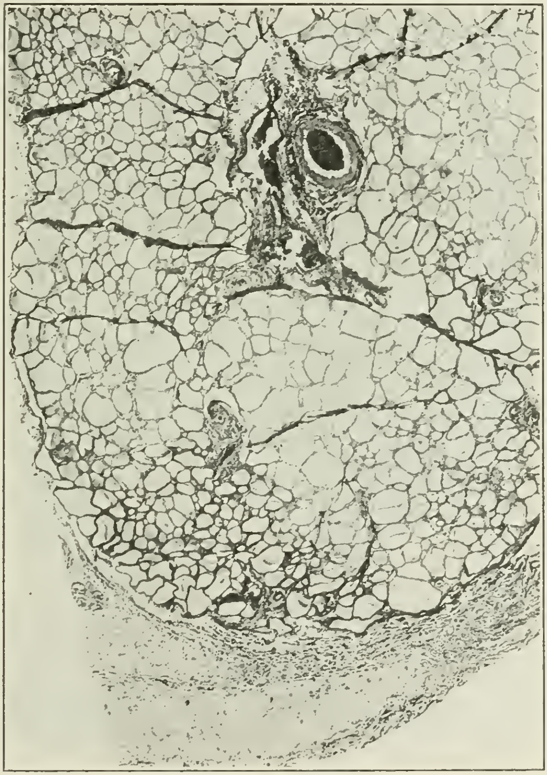

Fig. 1.—Dog No. 132. Autotransplantation thyroid with carotid and thyroid vessels. No thrombosis of vessels. Thyroid in normal state of preservation.

Parenchymatous organs of a more highly physiological function, such as the kidney, spleen, thyroid, etc., when transplanted into another animal, undergo autolysis and are eventually absorbed. The longest time a kidney has continued to functionate in an animal of the same species is three months (Stich, Ingebrigtsen).

Nemiloff found in transplantations on dogs that pancreatic tissue transplanted either as autografts or homoplastically, subcutaneously or intra-abdominally is for the most part absorbed in the course of a few days and that a thin zone of living parenchyma remains only at the edge of the transplant. This is more pronounced in homoplastic experiments. The longest interval of survival of any part of the transplant was fourteen days.

Crowe and Wlislocki, in their experimental work in suprarenal glands in dogs, found in several instances normal-looking viable cells of the cortex after transplantation, but the majority of grafts underwent degenerative changes and were eventually replaced by scar tissue; in any event the chromaffin elements entirely disappeared. The authors attributed these changes to the lack of nerve supply to the graft.

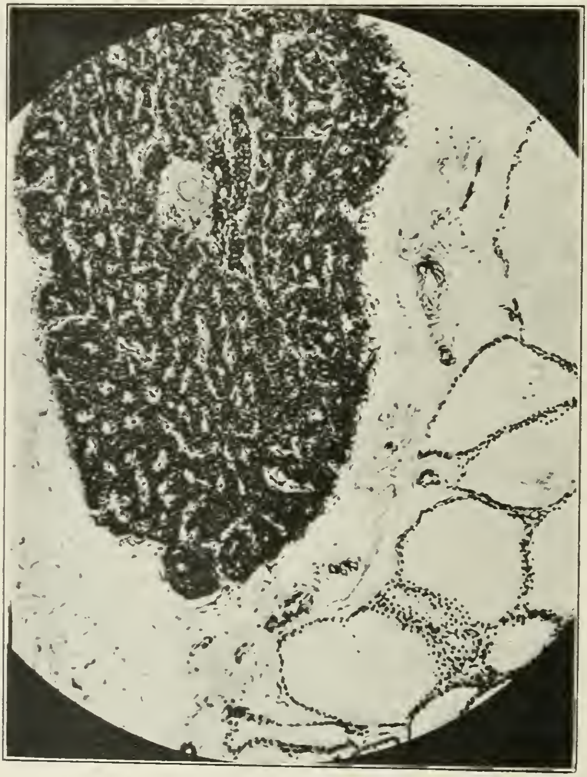

Fig. 2.—Dog No. 142. Homotransplantation of thyroid gland with carotid and thyroid vessels. Shows parathyroid in perfect preservation, but does not show how many oxyphil cells it contains. Vessels preserved in their normal state. Thyroid fairly well preserved.

Lexer remarked at the International Surgical Congress in New York, 1914, that he had been able to overcome some of the biochemical differences in animals by prolonged treatment of the host with serum and tissue taken from the donor. By these means skin transplants lasted considerably longer; in some cases even for six weeks. He considered that the prospects of improving homoplastic surgery were most hopeful along this path.

James B. Murphy found that if portions of the spleen were transplanted with the malignant tumor transplant that the growth of the latter was retarded. He reasoned, therefore, that if the activity of the lymphatic system could be temporarily retarded that the chances for the permanency of the transplant would be materially increased. He suggested either the application of Roentgen rays or the internal administration of benzol for this purpose.

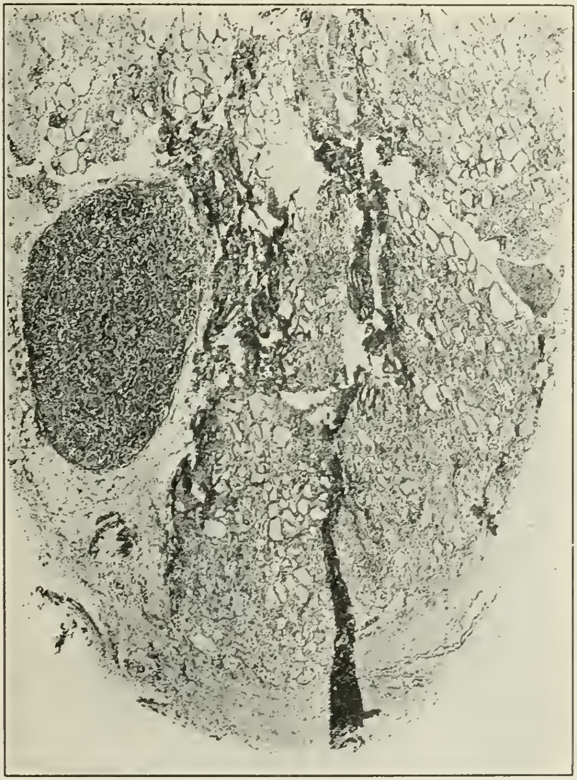

Fig. 3.—Dog No. 199. Homotransplantation thyroid with carotid and thryoid vessels. Colloid absent. Follicles extensively shrunken and destroyed. The parathyroid is not very well preserved, but shows no connective-tissue proliferation nor vessel changes.

Among the more recent attempts at transplantation in human beings the more remarkable are those of Tuffier, Kocher, Lydston, Payr, and Küttner. Tuffier did 204 ovary transplantations in which the autografts were only successful in women under forty years of age. In 4 cases Tuffier removed human autografted ovaries from two to three years after they were transplanted, and found incontrovertible evidence that they had been functionating. Tuffier concluded, however, that when the uterus is absent, ovarian transplantation is of no value.

G. F. Lydston, in his experiments with the testicle, had surprising results in therapy, but his transplants did not long survive.

Marine has demonstrated on rabbits that specific secretory nerve fibers are not essential in transplants in order that thyroid tissue may exhibit the characteristic morphological and physiological changes known to be associated with great variations in functional activity.

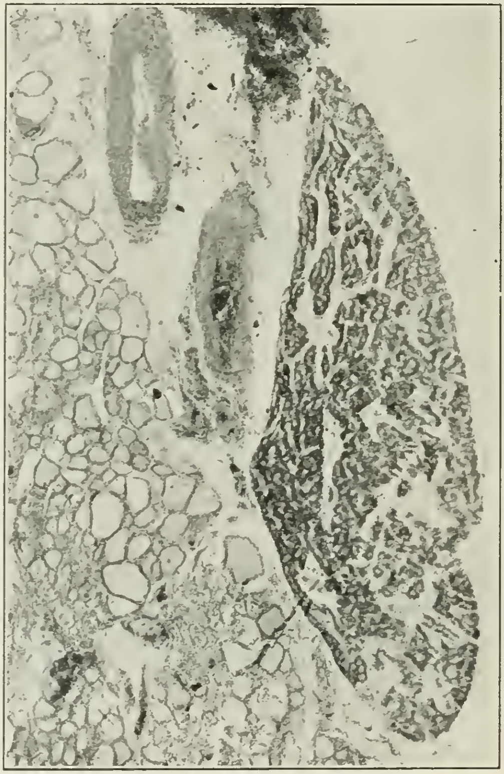

Fig. 4.—Dog No. 202. Homotransplantation of thyroid gland with segment of carotid and the thyroid vessels. Parathyroid gland in good state of preservation. Thyroid shows evidences of beginning autolysis.

Theodore Kocher and Payr concluded that thyroid transplantation was much more effective and more rapid than that of thyroid medication, but Kocher believed that one transplantation did not suffice. Kocher also believed that the problem of ensuring the permanency of the transplant might be solved by finding ways of decreasing the recipient's immunity and of performing the transplant in the presence of an infection.

Stich found that thrombosis of the thyroid veins was a menacing factor. When this occurred, some time after the transplantation, there was some chance of vascularization from the surrounding tissue; otherwise the transplant was lost.

With a view of throwing some light on the causes of failure in the transplantation of organs, we chose the thyroid gland for our experiments on account of its accessibility and the readiness with which it offers itself to reimplantation with a restoration of its circulation by the aid of bloodvessel suture. We found that we were able to overcome the difficulties of venous stasis and thrombosis by adopting the technic already referred to in *Annals of Surgery*, December, 1914. This technic consists briefly in an implantation of the thyroid gland underneath the muscles of the neck and a biterminal suture of a segment of the attached carotid of the severed vessel of the host and end-to-end suture of the thyroid vein with the central end of the external jugular of the opposite side.

TRANSPLANTATION OF THE THYROID GLAND WITH A SEGMENT OF CAROTID ARTERY

Dog No.		Condition of carotid.	Duration of life.
132	Autotransplant	No thrombosis	23 days
138	“	“	24 hours
142	Homotransplant	“	12 days
147	“	“	14 “
148	Autotransplant	“	4 “
157	Homotransplant	“	44 “
164	“	“	42 “
174	“	“	6 “
186	“	“	10 “
192	“	Partial thrombosis Gland absorbed	79 “
199	“	Thrombosis	4 “
208	“	No thrombosis	2 “
242	“	“	5 “
262	“	“	3 “
269	“	“	7 “
274	“	“	3 “
38	“	“	5 “
58	“	“	10 “
77	“	“	9 “
98	“	“	4 “
107	“	“	5 “
124	“	Partial thrombosis	4 “
180	“	No thrombosis	61 “
191	“	Thrombosis	49 “
202	“	No thrombosis	8 “
225	“	“	21 “
229	“	“	14 “
239	“	Partial thrombosis	7 “
283	“	Gland absorbed No thrombosis	53 “
214	“	No thrombosis	112 “

During the months of October and November, 1914, we had a series of postoperative hemorrhages. A microscopic examination disclosed a traumatic rupture of one of the lines of suture. Investigation proved that these hemorrhages were brought about by accidental fighting between the animals.

In Case 202 the carotid was smooth, the superior thyroid artery, the thyroid and external jugular veins were patent, and the gland and the transplant were normal in color and appearance. The capsule was smooth and freely movable. Death was due to pneumonia. The pathological report by Professor Symmers was as follows:

"The upper portion of the thyroid reveals the presence of numerous vesicles containing colloid, the interstitial tissues are not increased in thickness, and the gland appears to be normally vascularized. The lower portion of the thyroid shows the presence of a relatively low proportion of colloid-containing vesicles. The majority of the vesicles are empty of colloid. They are lined with a rather low cuboidal epithelium which in many places have undergone proliferation, partially filling the lumen of the vesicle. The desquamation of the epithelium occurs in places. The interstitial tissues do not appear to be thickened. The parathyroid gland is apparently well preserved."

There was not, in the entire series of 30 operations, a single instance of infection. In 12 of these cases, intratracheal anesthesia with the Janeway intratracheal apparatus was used. In the remaining cases ether was administered with an Allis inhaler.

We have had three instances among our homotransplantations in which the parathyroid gland remained in a normal state of preservation while the thyroid gland showed evidences of autolysis. In autotransplantation we have succeeded in two consecutive instances in retaining the thyroid gland in its normal state microscopically. On the transplanted bloodvessels we have made the following observations: In 25 out of 30 instances the segments of the carotid artery remained free from thrombosis and in 4 instances the superior thyroid artery also remained patent and without any evidences of thrombosis, although the gland transplanted has undergone autolysis and was partly absorbed. The histological findings of these specimens will be reported in a subsequent article.

We agree with Stich, Borst, Enderlen, Carrel, Lexer, and Jeger that autotransplantation is practicable. After homotransplantation the transplant of a bloodvessel will retain its life for an indefinite length of time while more highly organized tissue of a more complicated physiological function will remain intact for a short time only, from two to four weeks, and will then show evidence of absorption. In the absence of hemolysis and agglutination the life of the transplant of even more highly organized tissue may be prolonged. We must conclude that up to the present time we have no means of prolonging the life of an organ transplanted from one animal to another indefinitely.

Thanks are due to Dr. I. Seff and to Dr. S. Berkowitz for valuable assistance.

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GASTRIC FUNCTION IN PULMONARY TUBERCULOSIS.[1]

By Henry K. Mohler, M.D.,

and

Elmer H. Funk, M.D.,

PHILADELPHIA, PA.

(From the Department of Medicine of the Jefferson Medical College, Philadelphia, Pa.)

The importance of a study of the gastric function in pulmonary tuberculosis can scarcely be overestimated when we consider the great frequency with which symptoms of disordered function occur, and particularly when we recall the important part which the digestion plays in the successful treatment of these patients. The frequency of gastric symptoms has been variously stated by different writers; thus Hutchinson, among the older observers, emphasized the frequency of dyspepsia as an early symptom, stating that it occurred in 92 per cent. of his cases, and in 55 per cent. was quite severe. More recent observers give lower percentages, thus, Janowsky 35 per cent., Levison 74.6 per cent., and Landis 55.3 per cent. In our own experience we found among 1000 consecutive patients with pulmonary tuberculosis in various stages that symptoms referable to the stomach were complained of in 64.6 per cent.

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[1] Read before the National Association for the Study and Prevention of Tuberculosis, Washington, D. C., May 12, 1916.

While gastric disturbances are very common, the symptoms produced are not entirely due to changes in the stomach peculiar to tuberculosis, but, as Landis pointed out, are such as might occur in any chronic wasting disease. It is also a mistake to designate these disorders as purely functional, since catarrhal inflammation is commonly associated. Organic lesions other than catarrhal inflammation, such as ulcer, cicatrical stenosis of pylorus, etc., are extremely rare. This is in striking contrast with the alimentary tract below the stomach, in which ulceration, particularly, is extremely common.

It is not the purpose of this paper to present a discussion of the pathological changes in the stomach, nevertheless, a brief summary of these changes will aid in the interpretation of the symptoms and disordered functions. We know practically nothing of the pathological anatomy of the stomach in early tuberculosis. In advanced lesions, however, autopsy reveals frequently a chronic catarrhal gastritis with some degree of dilatation. W. S. Fenwick states that it is rare to do an autopsy on these cases without encountering some increase in the dimensions of the organ. Among 100 cases in which a special note was made of the position of the lower margin it was found below the umbilicus in 64. He believes that the degree of gastrectasis bears a direct relation to the extent and chronicity of the pulmonary lesion. In 6 out of 7 cases of acute miliary infection no increase in the size of the stomach was observed. The histological changes in the stomach are largely those of chronic catarrhal inflammation. The studies of Marfan, Schwable, Fenwick and others confirm this view. Actual tuberculous lesions of the stomach are extremely rare; ulceration, the most common, occurring but twice in 2000 autopsies at the Brompton Hospital (Fenwick) and not once in 85 autopsies among our patients.

We have endeavored in the present study to investigate primarily the gastric function in early and advanced cases of tuberculosis, and having obtained this information, to correlate disordered function with disease and symptoms.

The studies of Rehfuss, Hawk, and Bergeim and their co-workers in the Jefferson Medical College and hospital have demonstrated the fallacy of the old-time method of estimating gastric function by a single analysis of a test meal withdrawn one hour after ingestion by the large stomach tube with an aspirating bulb. The impossibility of interpreting the findings by this method depends upon (1) the inadequacy of the tube, and (2) the fallacy of single one-hour examinations. Harmer and Dodd have shown by Roentgen-ray studies that the old stomach tube does not completely remove the gastric contents. It is objectionable to the patient, causes considerable gagging and swallowing of mucus, and cannot be retained in the stomach with any degree of comfort for any length of time. The tube which overcomes these objections is a smaller one of a diameter of 4 mm., which at one end has a perforated metal tip sufficiently heavy to pass by gravity into the stomach and its lowest portion. After insertion the tube may be left *in situ* as long as necessary until the whole phase of the gastric digestion has been studied. By this means small quantities (8 to 10 c.c.) of gastric contents can be withdrawn at fifteen-minute intervals after the ingestion of the test meal and examined. By this method, termed "fractional estimation," a "secretory curve" can be established of considerable value in determining the gastric functions.

Practically all the recorded studies of gastric function in pulmonary tuberculosis, notably those of Edinger, Brieger, Klemperer, Schetty, Hildebrandt, Einhorn, and Immerman, were made by the old method, and are, therefore, in the light of new methods, open to grave criticism as to their accuracy and their interpretation.

Einhorn found in 15 cases that normal acidity existed in 5, hyperacidity in 5, and diminished or absent acidity in 5 cases. Klemperer, Immerman, and Schetty found in early cases that the secretion was normal or somewhat increased. Brieger found in the early stages that the cases of normal and disturbed secretion were about evenly divided; in moderate cases normal in 33 per cent., reduced in 60 per cent., and absent in 6.6 per cent.; and in advanced cases, normal in 16 per cent., reduced in 74.4 per cent., and absent in 9.6 per cent. Van Valzah and Nisbet found in 65 per cent. of 73 comparatively early cases that the secretion of HCl. was normal or above at least part of the time. Croner studied 36 cases of early tuberculosis and found the total acidity varied from 21 to 80, except in 5 cases, which showed a complete failure; in most cases, however, it was normal. Hayem studied 80 cases; among the 32 incipient, 15 showed hyperacidity, 16 hypoacidity, and 2 apepsia. Among 48 advanced cases 15 showed hyperacidity and 33 hypoacidity. Reed, in his book on *Diseases of the Stomach and Intestines*, states that "it is now known that a large proportion of the cases of early phthisis—a preponderance of them according to some observers—has an excessive secretion of HCl."

Klemperer found that free HCl gradually disappeared as the pulmonary disease progressed, while Schetty could discover no marked alteration, and Immerman was able to find it even in advanced cases with fever. Hildebrandt believed that fever played an important role, since he found HCl absent in pyrexia and present in apyrexia.

The motor function of the stomach was studied by Immerman and Klemperer. The former found no changes, while the latter, using his oil method, found a marked enfeeblement. Einhorn found that the motor power of the stomach was not diminished to a very high degree, and Brieger states that when the secretion of HCl fails there is a diminution in motor power. King studied 26 cases and found in active incipient cases that the acidity and motility are increased; in inactive incipient cases no uniform disturbance other than that found in non-tuberculous individuals; in advanced cases, active and inactive, the tendency to a lowered acidity and motility. One of King's cases showed achylia gastrica. Munson, in 1905, concluded a very excellent review of the literature and a personal study with the statement that the small amount of hyperacidity in his series, its occurrence in early as well as late cases, the marked tendency to hypoacidity and its frequent transformation into anachlorhydria, and the undisturbed motor power made up the picture presented by his cases.

The lack of harmony must be perfectly evident, and is due, perhaps, to the inherent fallacies of the old method of study of the gastric functions which we discussed in the early part of this paper.

Rehfuss, Bergeim, and Hawk found that in normal individuals no specific curve could be constructed that would include all cases free from gastro-intestinal symptoms. It was possible, however, to classify them according to one of the following three types:

1. The "isosecretory" type (Chart I), which shows a steady rise expressed in terms of cubic centimeters of tenth normal sodium hydroxide, maximum 60, usually sustained from half an hour to one hour, and then a gradual decline with a total disappearance of the food rests in from two to two and a half hours.

2. The "hypersecretory" type (Chart II) shows a rapid response to stimuli, often a marked change in the acidity, rapid rise in the acidity high point from 70 to 100 or more, either abrupt or sustained, and a slow or no decline in the usual time. The test meal left the stomach in normal time, that is, from two to two and a half hours; but even after the passage of all material there was encountered an outpouring of pure gastric juice for a half hour, one hour, or even several hours. This finding was so common in symptomless cases that Rehfuss and his coworkers called it "continued" digestive secretion in contradistinction to hypersecretion, which is a distinct clinical entity with symptoms.

3. The "hyposecretory" type (Chart VI) is similar to the first type, but there is usually a slower ascent, slower response to

stimuli, and a high point from 40 to 50. Rehfuss encountered this type least frequently in normal subjects.

The patients studied in our series comprise 22 early and 25 advanced cases of pulmonary tuberculosis.[2] The early cases were dispensary patients and the advanced cases were in the hospital wards.

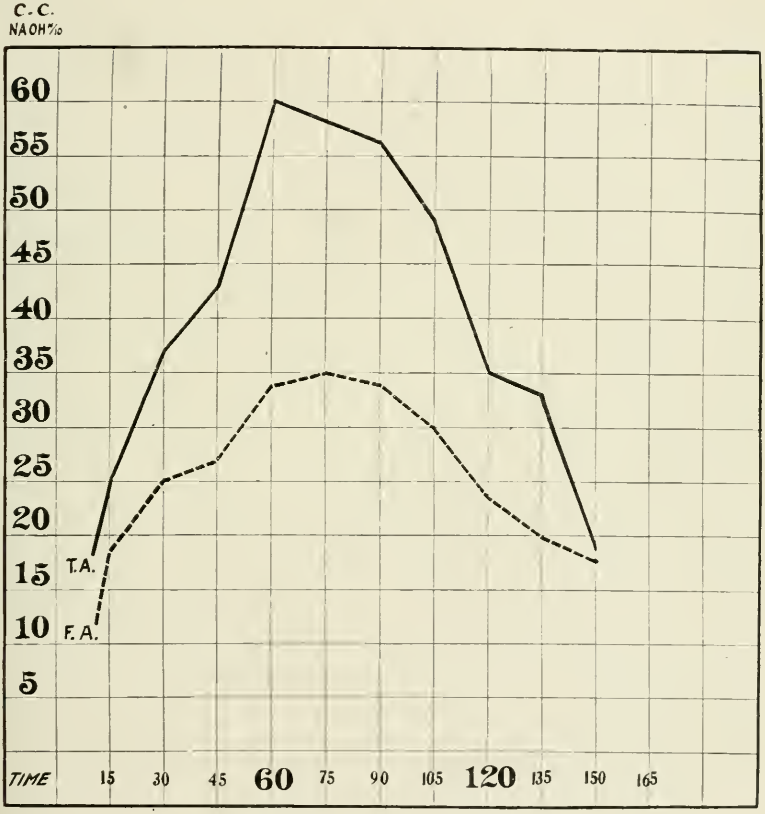

Chart I.—"Iso-secretory" type.

Early Cases. Among the 22 early cases observed, 11 complained of symptoms referable to the gastro-intestinal tract. Of this number 3 suffered with symptoms prior to and the remaining 8 subsequent to the development of cough, fever, etc., symptoms common in early lesions.

The gastric symptoms complained of in order of frequency were belching (which cannot be accounted for in every case by fermentation and was doubtless due to aërophagia), fulness and distress in the epigastrium, anorexia and vomiting.

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[2] The technic employed is described in Hawk's Practical Physiological Chemistry, 1916, 5th ed.

The high point of the total acidity (expressed in terms of the number of cubic centimeters of tenth normal sodium hydroxide required to neutralize 100 c.c. of gastric juice) was noted in

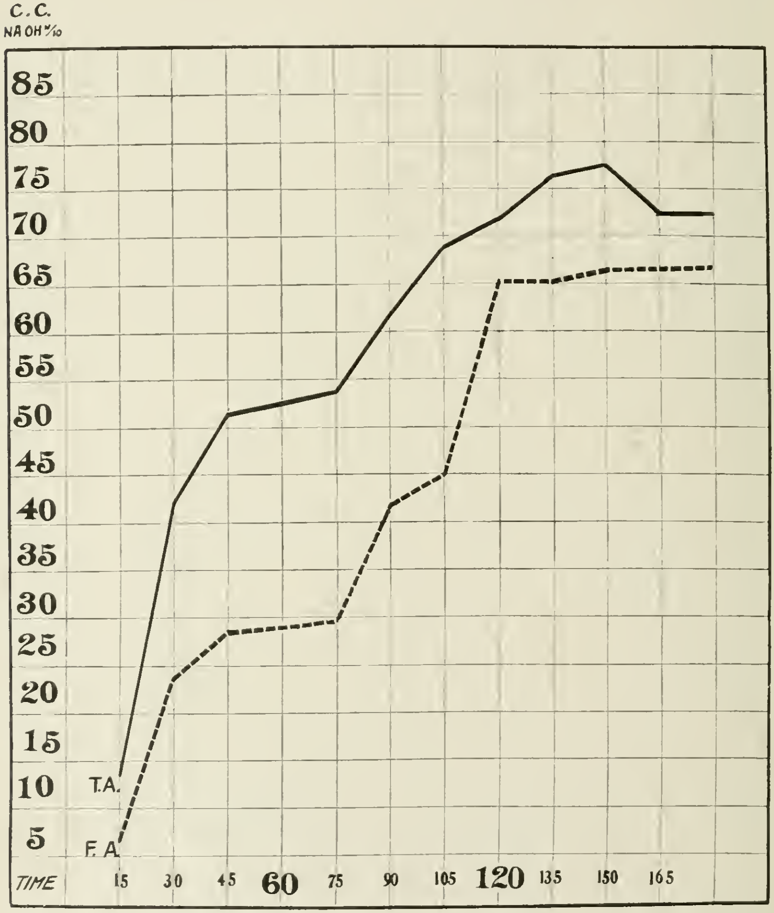

Chart II.—Hypersecretory type with continued digestive secretion; no symptoms.

6 cases at 1 hour
5 cases at 1¼ hours
4 cases at 1½ hours
3 cases at 2¼ hours
3 cases at 2½ hours
1 case at 2¾ hours

The high point of the free acidity (expressed in terms of the number of cubic centimeters of tenth normal sodium hydroxide required to neutralize 100 c.c. of gastric juice) was noted in

1 case at $\frac{3}{4}$ hour
4 cases at 1 hour
5 cases at $1\frac{1}{4}$ hours
2 cases at $1\frac{1}{2}$ hours
2 cases at $1\frac{3}{4}$ hours
4 cases at $2\frac{1}{4}$ hours
3 cases at $2\frac{1}{2}$ hours
1 case at $2\frac{3}{4}$ hours

It will be noted in the series of 22 early cases studied the high point of total acidity occurred at or before the one-and-a-quarter-hour period in 11 instances. Of these 11 cases, 3 presented gastric symptoms and 8 no symptoms. One may assume that where the high point occurs at the sixty-five or seventy-five-minute period, gastric symptoms are infrequent, provided the high point falls within the normal range of acidity. With regard to the 11 cases in which the high point of acidity occurred after the seventy-five-minute period, gastric symptoms were present in 7 instances and absent in 4; approximately a reversal of the former findings. The symptoms complained of in these cases occurred in the period preceding the high point. The explanation is that the symptoms are no doubt due to a delay and a deficiency in gastric function.

Nine of the 22 cases showed curves which revealed that after the Ewald test meal had left the stomach the secretion of gastric juice continued and the acidity remained high, as shown in Chart II, conforming with the "hypersecretory" type with "continued" digestive secretion.

After the administration of the Ewald meal, food rests were obtainable at the end of two and a half hours in 5 or 23 per cent. of the cases. We have been impressed by the lack of definite relation between gastric motility and gastric secretion. Case 19 (Chart III) of our series of early cases presents a curve of acidity with hypermotility in which the Ewald meal left the stomach at the end of seventy-five minutes and the patient did not complain of symptoms referable to the gastro-intestinal tract. Abderhalden and Meyer have shown active pepsin in all parts of the small intestine. This observation, coupled with the action of trypsin in the intestines, may account for the lack of symptoms noted in this case. On the other hand, in Case 20 (Chart IV), which type of curve conforms to the "hypersecretory" with "continued" digestive secretion, the high point of total acidity reached 124 at the one-hundred-and-fifty-minute period and presented no gastro-intestinal symptoms, while, at the same time, considerable remains of the Ewald meal were recovered.

Our observations have shown us that in patients presenting one of the normal types of secretory curves it does not necessarily follow that they possess normal appetites, but it is true that it is rare to note the reverse, that is, a normal appetite in patients exhibiting distinct pathological secretory curves. That the psychic element plays an important role in the creation of appetites of patients is very evident. Seven cases showed an excessive amount of mucus in one or more specimens or in the residuum. This condition occurred in patients complaining of gastro-intestinal symptoms. Lactic acid was present during the first hour in 9 cases. Bile was noted in the morning residuum of 6 patients. Free and total acidity were present in greater or lesser amounts in all the morning residuums. The peptic activity in early cases was not studied. No case of true hyperacidity with symptoms was encountered in the study of this series of early cases.

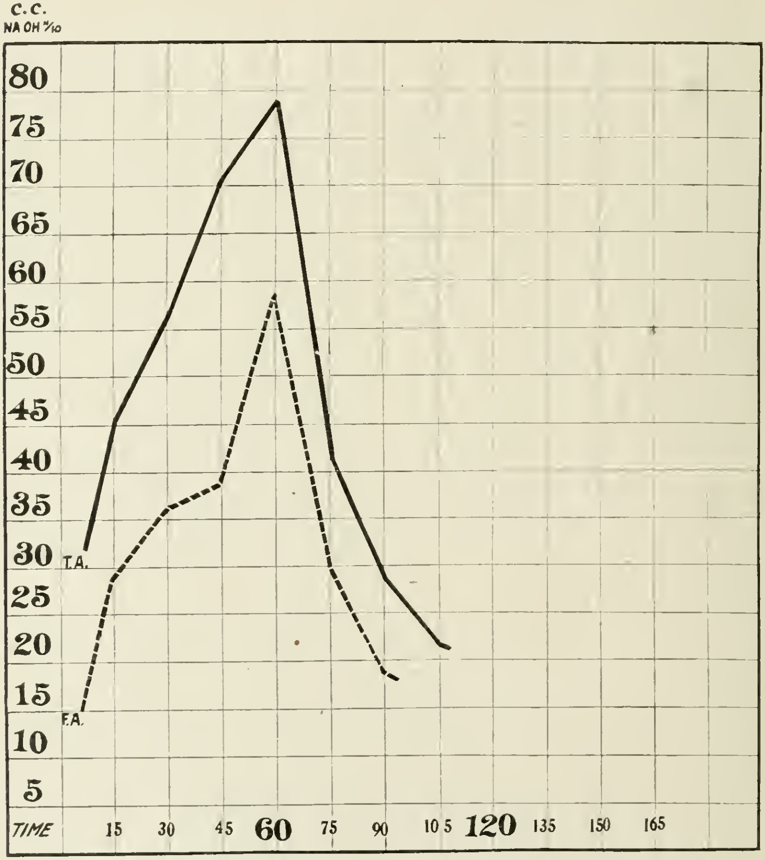

Chart III.—Hypermotility; absence of food rests after $1\frac{1}{4}$-hour period; no symptoms.

Advanced Cases. In a series of 25 advanced cases of pulmonary tuberculosis, 24 patients complained of gastro-intestinal symptoms. The morning residuum revealed the presence of mucus, bacteria, and leukocytes in excessive amounts in 20 of the cases. The tubercle bacillus was present in the residuum in 18 cases.

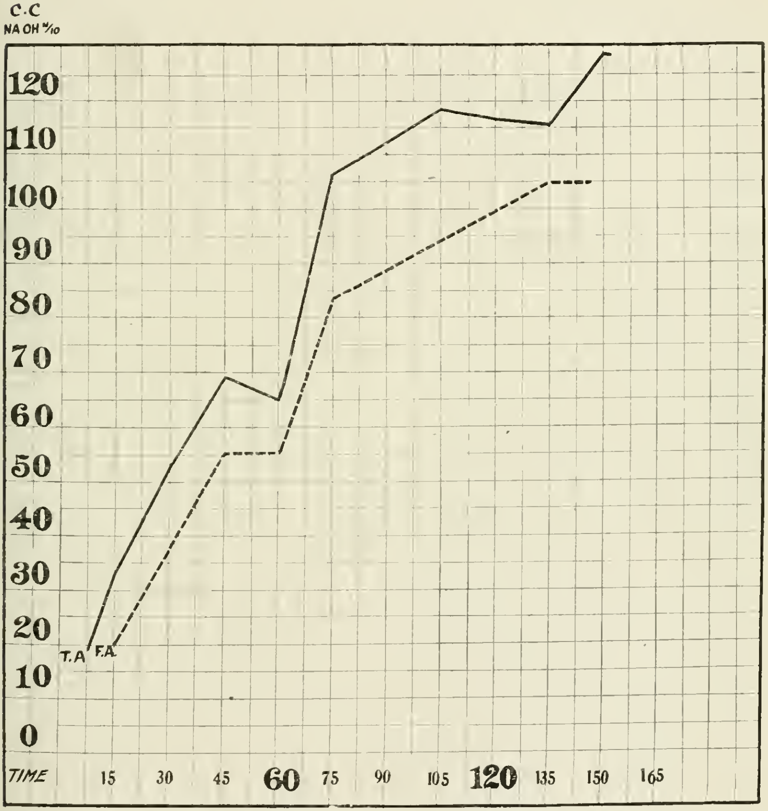

Chart IV.—Hyperacid type with continued digestive secretion; food rests at 2½-hour period-hypomotility; no symptoms,

The time of the occurrence of the high point of total acidity in this series was noted as follows:

1 case at ¾ hour
7 cases at 1 hour
3 cases at 1¼ hours
3 cases at 1½ hours
6 cases at 1¾ hours
5 cases at 2 hours

The high point in free acidity was noted as follows:

1 case at $\frac{3}{4}$ hour
5 cases at 1 hour
4 cases at $1\frac{1}{4}$ hours
5 hours at $1\frac{1}{2}$ hours
4 cases at $1\frac{3}{4}$ hours
6 cases at 2 hours

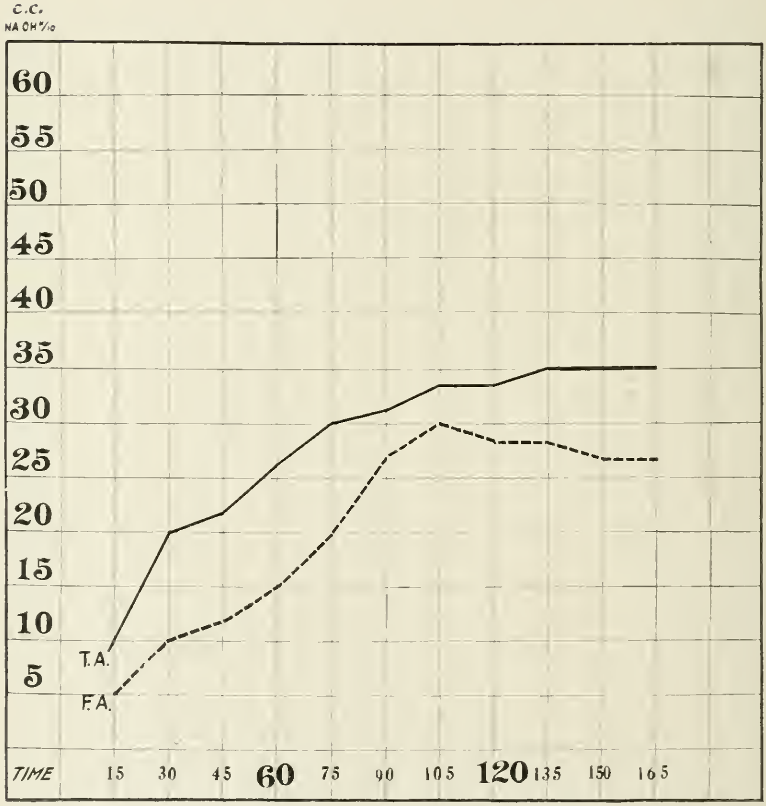

Chart V.—Typical curve showing delayed high point of acidity with continued secretion.

Fifteen of the advanced cases showed a slow ascent of curve with a late high point and continuation of the secretion rather than a decline, thereby resulting in delayed gastric digestion, as illustrated in Chart V.

After the administration of the Ewald meal food rests were obtainable at the end of two and a half hours in 18, or 72 per cent. of the cases, suggesting the greater frequency of delayed motility in the advanced cases as compared with early cases.

In 8 cases the curve conforms to the hyposecretory type, that is, a slow ascent to a high point which is sustained a half to three-quarters of an hour and then a gradual decline, as represented in Chart VI. The high point for total acidity in this group of cases averaged 24, and for free acidity 20, distinctly below the normal.

In one case we found a type of curve (Chart VII) representing psychic achylia in which the total acidity ranged from two at fifteen minutes to five at the end of one hour, with a total absence of free acid and peptic activity. Following this period the total acidity and free acidity rapidly rose to 40 and 32 respectively. Gastro-intestinal symptoms were very prominent in this case during the first hour following the taking of food. This case represents a type which by the older methods of gastric analysis would have been interpreted a case of true achylia gastrica rather than what we now know to be pseudo-achylia.

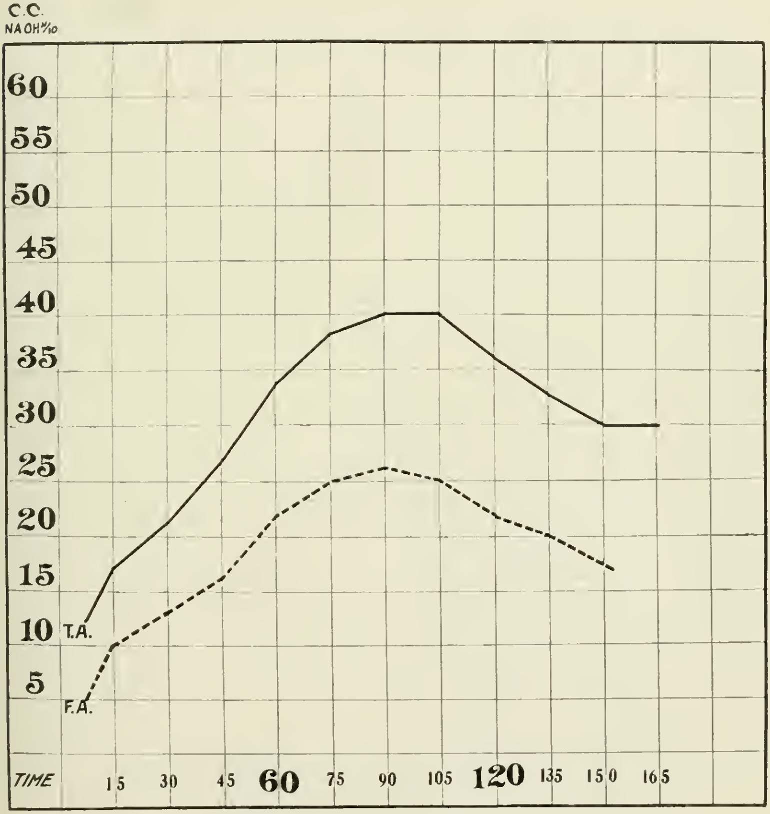

CHART VI.—Type of curve "hyposecretory" noted in 8 cases.

Only one case in this series of advanced cases—in fact, only one in the entire 47 cases of early and advanced—illustrates a type of "hypersecretory" curve with symptoms of hyperacidity, as shown in Chart VIII.

In the study of the peptic activity in 8 cases of advanced pulmonary tuberculosis it was noted that when the total acidity was low and slow in ascent the pepsin curve conformed to the acidity curve.

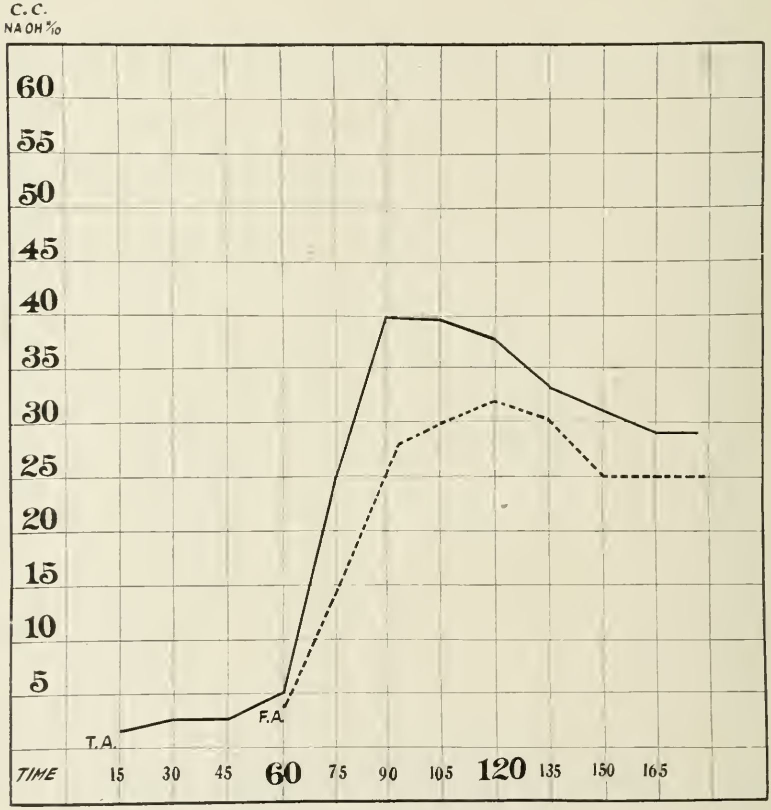

Chart VII.—Psychic achylia gastrica.

Conclusions. From a study of the early and advanced cases under observation we conclude:

1. That pulmonary tuberculosis causes a definite downward progression in both the motility and the secretory function of the stomach from the very beginning of the disease.

2. That hyperacidity with symptoms occurring in early stages and described by previous writers as common is quite rare. That even hyperacidity without symptoms is rare—the type which corresponds to the normal "hypersecretory curve" of Rehfuss

existing in 40 to 50 per cent. of normal individuals (Rehfuss) exists considerably less frequently in early tuberculous patients. This would indicate that even in early tuberculous patients, changes in gastric functions are present.

3. That the so-called "pretubercular dyspepsias" of previous writers are misnamed and that we believe they are in reality manifestations associated with definite tuberculous infection.

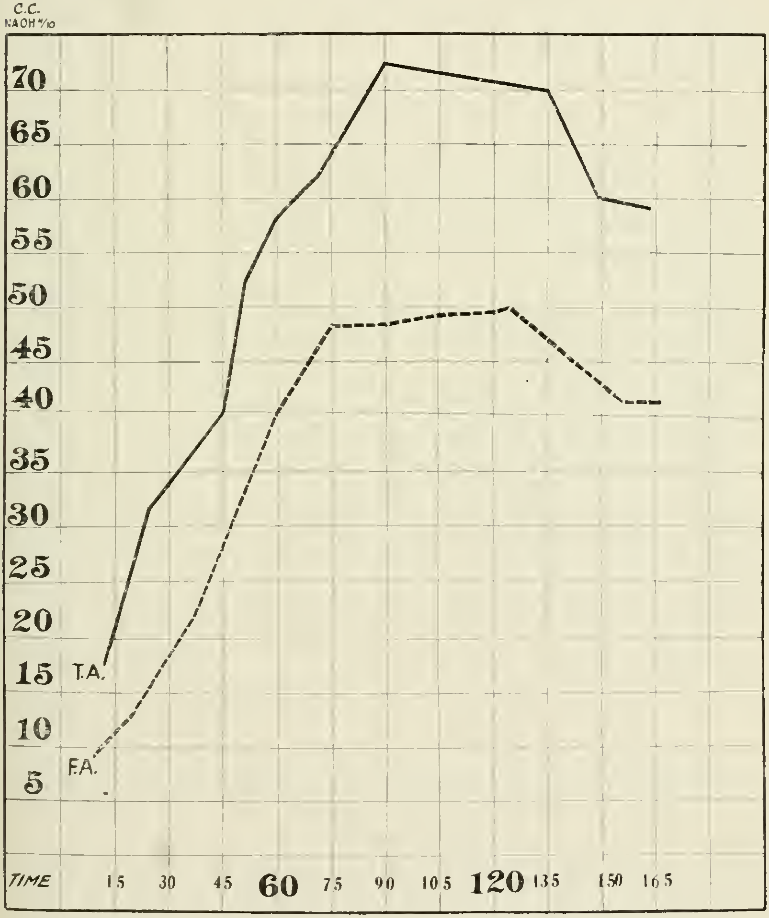

Chart VIII.—"Hypersecretory" type with symptoms of hyperacidity.

4. That we do not believe, on the basis of our studies, that there is an "irritative stage" giving hyperacidity in early tuberculosis. Our studies suggest that the gastric disorder is the result of disease of the gastric mucosa.

5. That there is a distinct tendency toward the formation of a definite clinical syndrome known as delayed digestion which becomes more and more associated with symptoms as the disease progresses.

6. We believe with Einhorn that the swallowing of tuberculous sputum plays a highly important role in the continuation and aggravation of disordered function. No less important are the visceroptosis and gastrectasis.

7. That the fractional estimation with the development of secretory curves is at present the most accurate method of studying the gastric function.

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INJURIES TO THE PERIPHERAL NERVES PRODUCED BY MODERN WARFARE.[1]

BY C. BURNS CRAIG, M.D.,
ASSISTANT PHYSICIAN NEW YORK NEUROLOGICAL INSTITUTE; NEUROLOGIST TO THE AMERICAN AMBULANCE, PARIS.

THE injuries to the nervous system which I shall describe are based upon ten months' observations at the American Ambulance Hospital at Neuilly sur Seine, and upon impressions gained by occasional visits to the Sal Pétrière and other Paris hospitals, as well as the hospitals nearer the front at Compeigne, Amiens, and Boulogne, and certain London hospitals.

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[1] Read before the joint meeting of the New York Neurological Society and the Section on Neurology and Psychiatry of the New York Academy of Medicine.

In classifying the cases in a large base hospital, it must be borne in mind that the proportion of injuries to vital parts as compared to less serious injuries does not represent the actual proportionate varieties of wounds occurring in battle; that is to say, the majority of men wounded in the brain, abdomen, heart, or large arteries die on the field or at the first-aid hospitals. Therefore, the majority, about 70 per cent., of the wounds in a base hospital are in the arms and legs. It is lacerations of the soft parts and fractures of the extremities that one encounters in a base hospital. I may say this is the only form of hospital in which the skilled man is necessary, as first-aid and transportation treatment can be carried out by men of common sense with a little medical knowledge.

It may be said that all wounds have a neurological aspect. The various kinds of pain and paresthesia, the cutaneous anesthesia immediately surrounding some large wounds, and the effect of the weather upon pain are worthy of attention had one the time to discuss them. Since the neurological feature in wounds is so universal it is evidently necessary to make more or less arbitrary classes of injuries to the nervous system. Therefore, by injuries to the peripheral nerves is meant only those in which a wound produced some marked paralytic effect distal to itself, indicating that one or more of the principal nerve trunks had been damaged.

Varying degrees of disability in the nerves below the point of injury are observed. The suspension of function may be due either to direct violence of the missile, flying fragments of bone, or to the resulting hemorrhage and edema of the part or to cicatricial pressure during healing. The subsequent disability may be motor or sensory, or both.

Mild cases of loss of function in the hand or foot from wounds with hemorrhage and edema in the extremity above them clear up rapidly, provided the part is not immobilized. It may be interesting here to cite a case of this class of a more severe grade:

J. D., aged thirty-three years, an excellent physical specimen, was wounded October 31, 1915, by a rifle ball which entered the right arm just external to the posterior axillary fold and passed inward, forward and upward, emerging immediately below the middle of the right clavicle. He was admitted to the hospital on November 3, having been over two days *en route*. The two wounds, each about the size of the end of a lead-pencil, were crusted over and apparently uninfected. The right arm looked normal, but the patient complained of stiffness in the elbow, wrist, and fingers, and there was considerable disability in these joints. The following day the disability was much greater, the entire arm was swollen and mottled, and there was well-marked hypesthesia. The arm was elevated, and the next day the dressing about the posterior wound was found saturated with bloody serum. In the course of a few days, with elevation and massage and passive movements, the arm resumed its normal size and the hand and elbow were again functioning. The skin of the arm assumed a light canary color, and went through the successive stages of discoloration characteristic of a severe bruise. A slow hemorrhage had evidently occurred into the soft tissues of the arm, and resolution occurred when this was literally emptied out at the bullet hole. Oozing continued for two weeks, the wound healed, and the joint stiffness and hypesthesia had almost disappeared by November 29, when he was discharged.

One of the greatest lessons learned in the war in taking care of wounds on a large scale is to avoid immobility of a wounded extremity. Even when a fracture exists with a large infected wound this may be avoided. The day is past when good treatment of a fracture consists in strapping the broken member to a splint or rendering the member motionless by plaster. In the early days of the war there resulted an abundance of cases styled "causalgia" by S. Weir Mitchell, and described by him as frequent following the American Civil War. In these cases the hand or foot is cold, darkly mottled, red and blue. The skin is of silky smoothness, glossy, and the hair has diminished, disappeared, or is of finest texture; the nails are long and curved. The joints are usually more or less ankylosed and the muscles wasted. The patient complains bitterly of more or less continuous burning pain of agonizing intensity at times, which is wearing and exhausting to the furthest degree. The application of moist dressings serves to keep the pain in abeyance, but when the skin again becomes dry the pain recurs.

It is interesting to quote a few lines from Mitchell's interesting book, *Injuries to the Nerves and Their Consequences*, in which he described with admirable accuracy numerous cases of causalgia in civil war soldiers.

"Looking carefully through my notes I find that in a considerable proportion of gunshot wounds of nerves there is principally burning pain, or at least that this is the prominent symptom, while in slight injuries of nerves from compression or contusions the other forms of pain are more apt to prevail.

"Perhaps few persons who are not physicians realize the influence which long-continued and unendurable pain may have upon both body and mind. . . . Under such torments the temper changes, the most amiable grow irritable, the soldier becomes a coward, and the strongest man is scarcely less nervous than the most hysterical girl. Perhaps nothing can better illustrate the extent to which these statements may be true than the cases of burning pain or, as I prefer to term it, causalgia, the most terrible of all tortures which a nerve wound may inflict.

"In cases of causalgia and glossy skin the hyperesthesia is due, I think, to nutritive conditions affecting the new surfaces and the nerves beneath them, so as to make the latter oversensitive. The tendency is toward atrophy and the thinned and shining skin, constantly fretted with tiny ulcers, seems at last to fail to shelter sufficiently its included nerve ends. Finally, the centres become oversensitive and radiate their state of sensitive wakefulness far and wide, just as in tetanus the motor excitability floods, at length, the nerves and more distant ganglia."

This condition is evidently due to immobilization of the arm and hand by the use of splints and slings in conjunction, of course, with varying degrees of injury to the nerve trunks. That such a result can be avoided has been amply demonstrated at the American Ambulance Hospital. An overhead suspension device whose detailed description must be left to the surgeon was used extensively on Dr. Joseph A. Blake's service, considerable study being given to alterations for individual cases by Dr. B. B. Neubauer. This contrivance provided elevation of the part, thereby diminishing the usual distal edema, and permitted sufficient movement of the hand to afford exercise without causing pain. This in conjunction with the early commencement of massage not only prevented the development of causalgia but shortened convalescence from four to six weeks.

Considering the enormous number of wounds of the extremities both of the bones and of the soft parts the infrequency of completely severed nerves is quite remarkable. This must be accounted for by the resiliency and elasticity of the nerve trunks, which permit a certain degree of displacement without rupture. Completely severed nerve trunks are comparatively rare, composing less than 10 per cent. of the cases of peripheral nerve injury. However, all the symptoms of a completely cut nerve may be present from severe contusion or compression of the nerve, and only by direct examination of the nerve at the site of injury, can the real nature of the injury be determined. The proportion of peripheral nerve injuries to the total number of wounded runs approximately as follows:

Musculospiral	12	per cent.
Ulnar	9	" "
Median	9	" "
Circumflex	5	" "
Internal cutaneous	4	" "
Sciatic	10	" "
Obturator	0.5	" "
Long saphenous	0.3	" "
Popliteal	2	" "

These injuries follow the same general rules which obtain in civil practice, *i. e.*, injuries to the sciatic nerve are much the most painful, whereas injuries to the nerves in the arm are more apt to result in motor paralysis. The commonest motor paralysis is that of the musculospiral, due doubtless to the location of the nerve close to the humerus. An explosive fracture of the humerus such as usually occurs from the contact of the modern rifle ball invariably almost without exception produces a paralysis of the musculospiral of greater or less severity. Very seldom is there an isolated injury of a nerve, but each case is a multiplicity of injuries to all the tissues composing the part struck and may include one or all the nerves in that locality.

A study of the varieties of wounds is of great interest, but the neurologist is interested more in their effect in parts distant from the wound. It would also be interesting to classify the causes of wounds to the nervous system, but this is of little value, as the variety received in any hospital will depend upon the character of the fighting at the time. That is to say, if the action is chiefly artillery the predominating cause of wounds will be fragments of shell and shrapnel ball. If the battle involves chiefly infantry movements the predominating cause of wounds will be rifle and machine-gun balls. In regard to bayonet wounds, suffice it to say that the vast majority of them are fatal, due to shock and hemorrhage. Very few bayonet wounds reach first-aid hospitals and practically none are observed in base hospitals. Let us now consider a few typical individual cases.

I shall describe such cases as will best represent the result of severe contusion, partial division, and complete division of the principal peripheral nerve trunks.

Case 1.—The first case is one in which the glossopharyngeal nerve was wounded peripherally.

The patient was about 30 meters from the opposing trench on January 2, 1915, when a rifle ball passed completely through his head in a most symmetrical manner, entering the right cheek 2.2 cm. anterior to the attachment of the lobe of the ear and making its exit at an exactly symmetrical point in the opposite cheek. Besides having passed through the rami of the lower jaw and the masseter muscles it had traversed the soft palate at its junction with the hard palate, producing a small transverse slit 2 cm. long in the middle of the soft palate, just at its attachment to the bony palate. There was no other wound visible. The palate moved symmetrically and promptly when elevated, but the uvula continued to swing in a perpendicular line.

There was anesthesia of the soft palate below the wound passing out diagonally between the last molar teeth on either side. There was also anesthesia of both pillars of the fauces and the tonsils. The bite of the patient was impaired but the jaws could be closed; the grinding motion was also preserved but weak.

In the course of a few weeks the wound in the palate healed as did the external wounds. Although his ability to chew improved, there was no improvement when I saw him last, two months after his injury, in the paralysis of the uvula.

Case 2.—The following case is one of contusion of the facial nerve with recovery.

The patient was a man, aged twenty-five years, wounded by a rifle ball on March 5, 1915, which entered 2 cm. above the angle of the right jaw, shattering the ramus and causing a crack extending to the condyle, according to the Roentgen ray. The ball then coursed through the nasopharynx and made a notch in the left malar bone, fracturing the rim of the left orbit.

At the time of admission, March 30, 1915, having been in a front hospital previously for about a month, he was still slightly confused and inclined to be taciturn. Both sides of his face were swollen; there was distinct crepitus of the left malar bone and pain at the right angle on movement of the jaw. Besides these features there was a marked diminution in the activity of the muscles of the right side of the face upon both voluntary and emotional effort, which did not amount to complete paralysis. There was very little disability in the two sides of the frontalis muscle. He could not close the right eye nor move the right cheek and corner of the mouth to any great degree. He was unable to hear a watch at the right ear, and only at the left when held against the ear. Air conduction was better than bone conduction on the left side. There was no disturbance of his tongue or eye.

The patient's confused state gradually disappeared, and he was able to state that the ball had been removed in the front hospital through the mouth. There was gradual improvement in all his symptoms except the deafness in the right ear, so that in two months there was complete return of the motor power of the right side of the face. He could close his eyes completely and firmly, although the right lid lagged a little in promptness. The right side of the mouth and cheek were completely restored as to motor function.

I saw him the last time June 2, three months after his injury, and he was still deaf in the right ear, although hearing had returned in the left. There was considerable stiffness in the right mandibular articulation, so that he could only open his jaws 3 cms.

Case 3.—The following case is a rather frequent type of head injury, peculiar in that the chief disability consists of a motor paralysis of one side of the face.

The patient, an able-bodied officer, aged twenty-five years, wounded, September 1, 1914, by a rifle ball at 150 meters, which struck him 0.5 cm. from the left corner of the mouth, knocking out a tooth, traversing the mouth, cutting the left half of the tongue, and passing out through the right ramus of the lower jaw, just behind the last molar tooth, fracturing the jaw and tearing away part of the lobe of the ear and the surrounding tissues.

He presented at the time of admission, two days after his injury, a complete peripheral paralysis of the right facial nerve. He could not close the right eye nor move the right side of the mouth or face. The right half of the forehead remained smooth when attempt was made to wrinkle it. There was a small area of anesthesia over the right side of the chin.

The fracture in the jaw united without complication, the tongue healed up as did also the wound at the attachment of the ear.

This patient was kept under observation for a period of four months without any noticeable alteration in the paralysis. The anesthesia on the chin was doubtless due to loss of function in the mental branch of the right inferior dental nerve, which was caught at the sight of fracture.

Inasmuch as repair of the severed facial nerve would have been chiefly for cosmetic reasons it was decided not to attempt it until after the war.

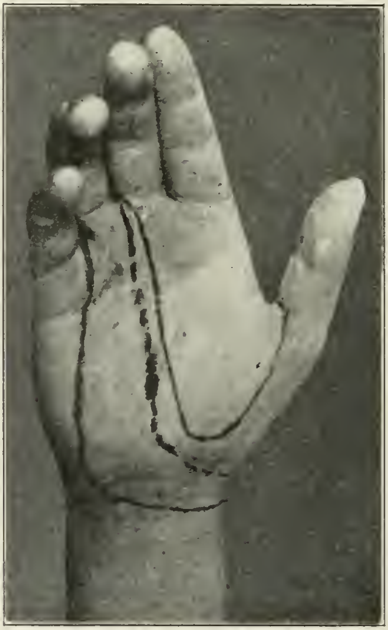

Fig. 1.—Case 4. Severe contusion of the median and musculospiral nerves. The outer line includes the area anesthetic to touch; the broken line, anesthesia to pain and temperature, and the inner line anesthesia to pressure. Note the thickened skin with faulty desquamation over the thumb and two first fingers.

Case 4.—The following case represents a group of cases in which the median and muscular spiral nerves were injured by contusion.

The patient was a young man, aged twenty-five years, wounded November 10, 1914, by a rifle ball at 150 meters. The ball entered 6 cm. above the external condyle and 5 cm. anterior to the perpendicular line from the condyle and passed diagonally upward through the arm and in front of the humerus making an exit

13 cm. above the external condyle in the perpendicular line of the condyle.

He suffered from continuous oozing from the wound of exit, and finally a severe hemorrhage occurred on November 15, so that it was necessary to ligate the brachial artery, which was done by Dr. Everingham. Recovery as regards the wound then proceeded normally and the wounds were fully healed by January 15, 1915. At that time the following paralytic phenomena were present: inability to flex the wrist toward the radial border; ulnar flexion was preserved; palmar flexion of the wrist was accomplished almost solely by contraction of the ulnar muscles. When at rest the hand inclined toward the ulnar side. The hand could be extended to a straight angle but no farther, and offered very little resistance, being easily forced into flexion. Opponens and adductor power of the thumb were wanting; there was feeble abduction and extensor power in the thumb. The two ulnar fingers could be flexed at the first phalanx, the distal two remaining extended. There was no flexor power in the index finger and very feeble in the middle finger. Abduction and adduction of the little finger were well preserved; it was feeble in the ring finger and absent in the other two. Triceps reflex was active, but the reflex in the biceps and suppinator were wanting. The reflex was also active in the extensor longus pollicis.

The skin over the radial border of the hand, front and back, showed improper desquamation in the form of a thickening and piling up of the epidermis. There was an extensive anesthesia of the palmar surface, as indicated in Fig. 1, to all modalities of stimulation. The outer line confines the area of anesthesia to touch, the interrupted line pain and temperature, the inner line pressure.

The patient was operated on January 26 by Dr. Drennen. The median nerve was found greatly swollen and edematous; musculospiral was less so. There was no anatomical interruption in continuity. The surrounding tissues were soft and friable, and it was difficult to control hemorrhage.

The patient recovered from the operation and improvement in the paralytic phenomena was exceedingly slow—in fact, during two months, after which the patient was lost sight of, there was very little, if any, improvement.

Case 5.—The next case is also one of contusion of the median with laceration of the ulnar nerve.

The patient was a vigorous young man, aged twenty-six ,wounded by bursting shrapnel on October 29, 1914. There were numerous pieces of shrapnel in the scalp and soft part of the arm. The major part of the olecranon process was blown away and the elbow joint exposed. The wound was cleaned up October 31, and the pieces of shrapnel removed. The arm was put in plaster for a month with drainage and the wound healed kindly, giving, of course, an ankylosed elbow. Examination showed at that time, December 1, a tender ulnar and median trunk in the arm. There was no area of anesthesia in the hand or forearm, but there was a pronounced hypesthesia over the ulnar portion of the dorsum of the hand, and over the palmar surface from the ulnar border to the middle of the palm, including the little and ring finger. The epicritic sense was lost distally to the first interphalangeal joint of the little and ring finger.

The skin of the fingers, especially near the tips, was thickened and brownish, and over the remainder of the hand the skin was mottled, cold, and moist; a pin-prick showed a small red point for a long time, which continued to bleed, and desquamation proceeded imperfectly. The nails were long and curved both laterally and from the matrix to the free border. There was a very incomplete flexor ability of all the fingers and thumb of the hand. There was no opponens power in the thumb, and abduction and adduction were imperfect.

A diagnosis of lesion of the ulnar nerve and damage to the median was made, and the patient was operated on December 5, by Dr. Blake. At operation the radial border of the ulnar nerve was found severed and a neuroma the size of the end of a finger had formed at this point. The median nerve presented a normal appearance. The neuroma was removed from the ulnar and the nerve was freed from scar and the raw ends of the nerve approximated. The operative wound healed without complication. Immediately after the operation there was a complete anesthesia over the entire distribution of the ulnar nerve, which was only hypesthetic before, and complete motor paralysis of both the ulnar and median, *i. e.*, of flexor power in the hand or fingers. Sensation slowly returned during the next five months, so that at the time he was last examined, April 11, 1915, sensation to touch, pain, temperature, and pressure had all returned; but there was atrophy of both the thenar and hypothenar eminences and the interosseous muscles and weakness of all the flexor muscles of the hand and fingers, more pronounced in those supplied by the ulnar. His elbow had, of course, remained ankylosed.

In this case the recovery of the contused median was almost complete at the end of five months, whereas the partially severed ulnar showed only partial and faulty recovery. The improvement was due, doubtless, to the resumption of function by the undivided portion of the ulnar.

Case 6.—The following case is one of isolated injury to the median.

The patient was a young man, aged twenty-six years, shot February 1, 1915, by a rifle ball while stringing barbed wire before his trench near Ypres, which was 50 meters from the trench of the

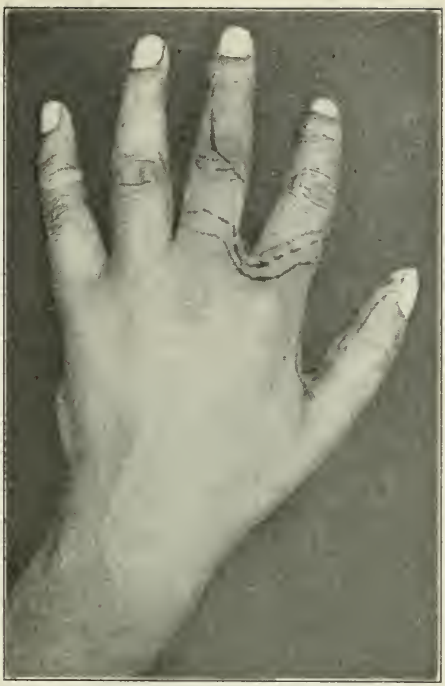

FIG. 2.—Case 6. Division of the median nerve in the middle of the forearm. The lower line limits anesthesia to touch; broken line, pain and temperature; upper line, pressure sense.

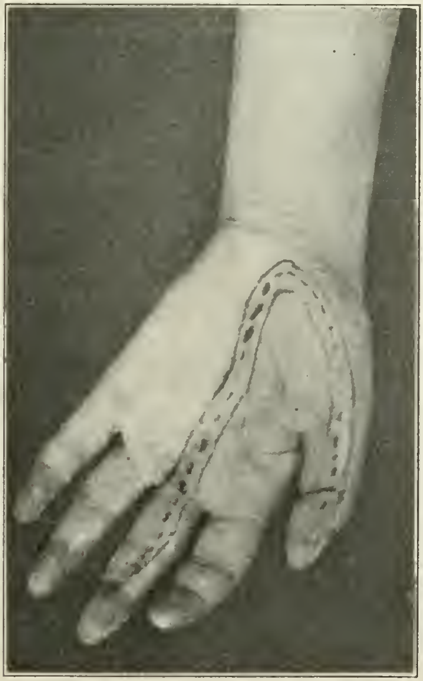

FIG. 3.—Case 6. Division of the median nerve in the forearm. The outer line limits anesthesia to touch; broken line, pain and temperature; inner line, pressure.

enemy. He felt no pain, but experienced a sudden paralysis of his left hand. He entered the hospital on February 3, 1915, at which time his left forearm exhibited, near the middle at the flexor surface, a small wound about 1 cm. in diameter, and upon the extensor surface immediately opposite was a wound about twice as large. The ball, which was evidently from a rifle, had passed through the forearm between the bones; the Roentgen ray showed no fracture. There was a slight yellowish desquamation around the wounds, but no infection, and they healed quite promptly. There was a paralysis of the flexors of the index and middle finger, none of the other two. He could oppose the thumb, and all extensor power in the hand was preserved. The end of the thumb and the first two fingers felt dead to him. Upon sensory examination there was found to be an anesthesia to touch, pain, temperature, and pressure over the palmar surface of the radial half of the hand and of the dorsum of the index and ring finger. (See Fig. 3.) Ten days after he was wounded he began to have a prickling sensation in the thumb and first two fingers. This patient was soon lost sight of, so that the outcome is unknown.

Case 7.—The following case illustrates the large group in which there was contusion of the musculospiral nerve.

The patient was a man, aged twenty years, wounded February 1, 1916, by a bursting shell. The missiles had shattered the humerus 10 cm. above the elbow and cut across the belly of the carpi-ulnaris group. Complete wrist-drop with no extensor power in the fingers resulted. There was moderate hypesthesia over the radial half of the dorsum of the hand. By June 1, 1915, after four months, he could extend the fingers slightly and the hypesthesia had diminished greatly. After five and a half months he began to extend the wrist, and by August 1, 1915, six months after the trauma, his wrist extension was fairly strong and that of the fingers practically normal.

Case 8.—This case showed complete division of a musculospiral and a great sciatic nerve.

The patient was a man, aged twenty-three years, wounded September 25, 1914, by a bursting shell. He fainted and fell. When he recovered consciousness, as he lay upon the ground, he found that he could move neither the right arm nor leg. He was transported by stretcher, train, and ambulance to the hospital, arriving September 27, 1914. He presented a badly comminuted, compound fracture of the humerus, together with a rifle-ball wound through the soft tissues of the thigh posterior to the femur. His wound was seriously infected with a gas bacillus, and he ran a very precarious febrile course for ten days, after which the infected state ameliorated. His arm went on to fair recovery as far as the fracture of the humerus was concerned, but continued to discharge purulent material up to February 13, 1915.

The wound in the thigh was thoroughly cleaned and healed up with greater promptness.

The hand presented a complete wrist-drop with no power of extension in any of the fingers or wrist. When attempting to grip something there was a marked tendency of the wrist to curve inward; the triceps reflex was absent. The hand continued cyanotic, moist, and slightly edematous throughout observation.

There was an anesthetic area, somewhat the shape of a mitten, over the dorsum of the hand, from the wrist to the base of the first finger, and including the thumb. Inside this area of anesthesia to light touch was a similar area anesthetic to temperature and pain; within this there were points where pressure was not observed.

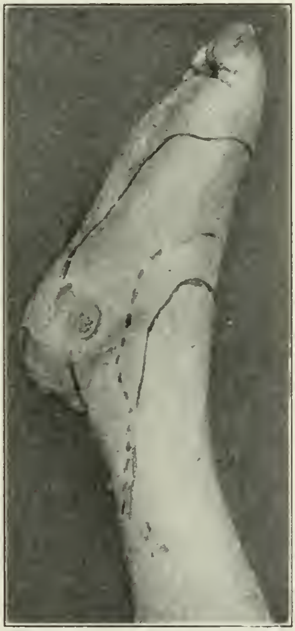

Fig. 4.—Case 8. Division of the great sciatic nerve. The line on the leg limits touch anesthesia; the broken line pain and temperature, and the line crossing the sole pressure anesthesia. Note the trophic ulcer.

There was also complete foot-drop with absence of the Achilles jerk and anesthesia over the dorsum and sole of the foot and the outer and posterior surface of the leg running up near the head of the fibula. The area of greatest extent was anesthetic to light touch; inside this was the area anesthetic to pain and temperature, while the absence of the pressure sense was confined to the foot. Over the inner surface of the leg from a point just below the ankle, sensation was normal.

The ball had entered the right thigh 10 cm. above the popliteal fold at the inner side and made its exit 19 cm. above the external condyle.

There developed during the next three months a considerable atrophy of the right thigh and calf, measurments being: right calf, 29 cm., left, 34 cm., at a point 13 cm. below the patella; right thigh, 45 cm., left, 51 cm., at a point 22 cm. above the patella.

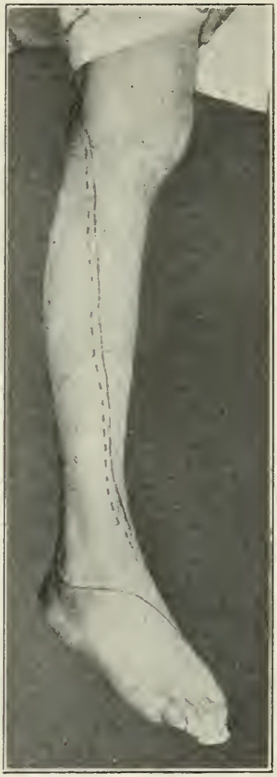

FIG. 5.—Case 8. Division of the great sciatic nerve. The long line limits touch anesthesia; the broken line pain and temperature, and the line crossing the foot pressure anesthesia.

The reflexes were, of course, present upon the left side, but the right knee-jerk was more active than the left. The right ankle-jerk was absent. There was no nerve-trunk tenderness.

On March 1 the sciatic nerve was exposed and found completely severed, and a large bulbus neuroma, the size of the last joint of a man's thumb, had formed upon the end of the upper fragment; the lower end was imbedded in dense scar tissue. A fragment of the sheath of the nerve remained intact and prevented the ends from becoming widely separated. The scar tissue and neuroma were removed and the cut ends of the nerve united.

During the course of the next month the patient developed trophic ulcers upon the right heel, dry desquamating surfaces with hard definite borders and pinkish centres, deepening into red at the middle. The skin of the sole became soft, smooth, and glistening. These trophic ulcers continued during the five successive months during which I had him under observation. They had appeared apparently without external injury.

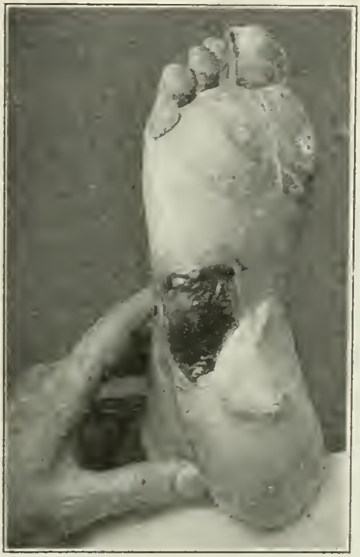

Fig. 6.—Case of severed sciatic with large trophic ulcer on the sole. The epithelium separated in one piece exposing a thick crust of dried yellow exudate into which hemorrhage had occurred. Complete anesthesia as in Case 8.

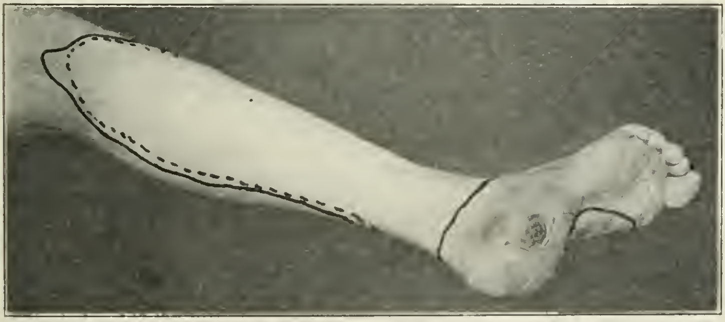

Fig. 7.—Case 8. Division of the great sciatic nerve. The long line limits anesthesia to touch; the broken line anesthesia to pain and temperature, and the line at the ankle anesthesia to pressure. Note the trophic ulcer.

The musculospiral was operated March 24 by Dr. Dubouchet and found to be severed completely with a large neuroma at the end of the upper frequent. This was removed, the ends of the nerve were freshened, all scar tissue was taken away and the nerve sutured. The wound of operation healed without noteworthy event.

During the succeeding five months following the sciatic operation and the four months following the musculospiral operation I observed no alteration whatever in the paralysis of either nerve.

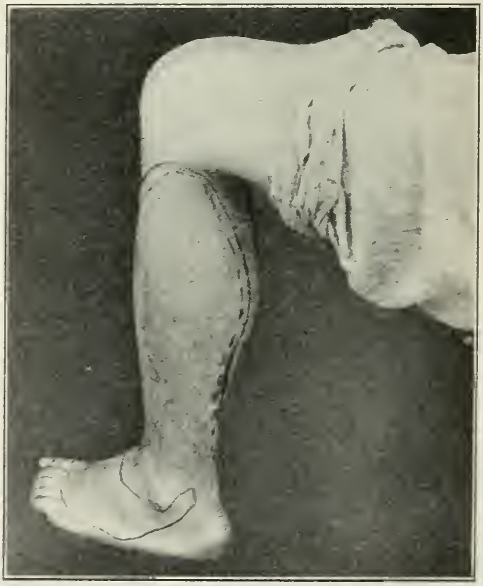

Fig. 8.—Case 9. Perforation of the great sciatic nerve by a shell fragment. The long line indicates anesthesia to touch; the broken line, anesthesia to pain and temperature. The area over the dorsum of the foot yields a burning sensation when a pin is drawn over it.

Case 9.—In the following case the sciatic nerve was completely traversed by a small fragment of shell without section of the body of the nerve.

The patient was a well-developed muscular man, aged twenty-two years, who came to the hospital March 14, 1915. He was wounded by an exploding bomb on March 2. He was thrown to his knees from a standing posture but was able to arise and walk 100 meters without pain. He noticed that his left foot drooped from the ankle so that he had to step high in walking. When he reached the aid post he was carried to the rear because severe pain had commenced in the sole of his foot, which made walking impossible. He continued to have severe pain of a burning character in the sole and outer side of the calf up to the time of admission. These symptoms were greatly increased by attempting to walk. At the time of admission he could, with considerable pain, bear his weight on the left foot, but could only take two or three steps.

Examination showed complete foot-drop with tenderness of the external popliteal nerve, also of the posterior tibial, and of the plantar nerves. The peroneal nerve was insensitive to compression. The Achilles jerk was absent and there was anesthesia to touch, pain, and temperature over the outer surface of the calf, sole, and toes. Over the dorsum of the foot and swinging round beneath the malleolus, like the neck of a pear, was an area over which the drawing of a pin-point produced a burning sensation. There was 1 cm. of atrophy in the left calf. Four centimeters above the flexus of the knee, just inside the outer hamstring tendon, was a small healed scar, about 1 cm. in diameter, which was exceedingly tender on pressure. A Roentgen-ray examination revealed a small piece of steel, about as large as a grain of wheat, at this point deep in the thigh.

At operation by Dr. Chauveau, on March 29, a deeply pitted scar was found in the sciatic nerve just above the bifurcation. The nerve was split but no foreign body was found; the missile had evidently passed completely through the nerve. For three days after the operation the pain in the leg was greatly diminished, but then recommenced with great vigor, and from that time gradually subsided and disappeared, so that by April 10 the pain was gone and the anesthesia, to all forms of stimulation, had disappeared except over the outer edge of the sole, where a pin-prick was still unperceived. The calf and external popliteal nerves were still tender on pressure. When the sciatic was compressed above the lesion paresthesia was produced in the foot. This condition did not exist previous to the operation.

By May 7, 1915, he was able to move the toes up and down feebly. While in bed there was no pain in the foot, but when it was dependent it became red and congested and painful, so that he could not step upon it. This condition proceeded for upward of six weeks before he was able to get about with comfort on a crutch, and it was another month before he could walk alone with any comfort.

Even in this comparatively slightly damaged sciatic nerve it was five or six months before recovery could be said to be approximately complete.

Case 10.—The following case will represent a group of cases in in which the sciatic nerve was almost completely cut across.

The patient was a vigorous man, aged twenty-four years, who was shot through both thighs near the middle and posterior to the femurs, October 5, 1914. The wounds were evidently those of a rifle ball. He was unable to move either lower extremity below the knee from the moment of injury. He was taken by stretcher and ambulance to the train and arrived at the hospital October 9. The wounds were mildly infected, but under antiseptic treatment healed rapidly. He presented a complete paralysis of the left foot, with foot-drop and absence of the Achilles jerk. There was no power in the anterior tibial or peroneal muscles. The gastrocnemius showed a feeble contraction of the inner half. Over this leg there was an area of anesthesia to touch, pain, temperature, and pressure covering the peroneal surface of the leg but narrowing sharply to a point near the head of the fibula. The heel, sole, and dorsum of the foot were also anesthetic. There was a small area of anesthesia over the peroneal surface of the right calf.

During the following month the area of anesthesia disappeared and motor power began to return in the right foot, but there was no improvement in the left leg. The popliteal nerve and its branches were extremely sensitive to pressure, especially the external peroneal.

During the second month the motor power became increasingly strong in the right foot, but there was no change in the left. The internal popliteal became less sensitive to pressure and the posterior tibial and plantar nerves became insensitive. During all this period the knee reflexes were active.

On January 15 Dr. Miniot cut down upon the left sciatic and found it all but severed and surrounded by dense cicatrix. There was a fine strand of anatomically intact nerve at the inner border. The cicatrix was completely removed as well as a large neuroma upon the upper end of the nerve, the ends of the nerve united, and the wound closed.

During the succeeding seven months there was not the slightest alteration in sensation or motor power in the left leg. About six months after the operation the patient spilled some warm water, not really hot, upon the dorsum of the foot, producing large blebs wherever the water fell; this resulted in a slowly healing trophic ulcer. The skin of the sole became thin, smooth, and papyrus-like. There was, of course, entire loss of sense of position in the toes.

Case 11.—This case was one of compression of the popliteal nerve, with complete recovery.

The patient was a well-developed young man, aged twenty-one years, wounded March 30, 1915, by a piece of shell which entered the thickest part of his right calf near the posterior median line, passed forward and lodged between the bones of the leg, as shown by the Roentgen-ray. Five days later, because of severe hemorrhage, while lying in a hospital near the front, the popliteal artery was ligated.

He entered the American Ambulance April 18, 1915, and presented a complete foot-drop without any extensor or flexor power of the foot or toes. There was also complete anesthesia of the sole and the peroneal surface of the leg and of the dorsum of the foot, except a triangular space running from the little toe to the ankle, then to the heel. Over this area sensation was preserved; the Achilles reflex was absent. The roentgenogram showed a piece of shell to be still present. On April 23 this was removed by Dr. Chauveau.

By the middle of May the wound had healed. At this time the Achilles reflex was found to be again present, though feeble; feeble flexor power of the foot and toes was also present and the foot could be feebly inverted, *i. e.*, there was *no* extensor power. The anesthesia had become rather marked hypesthesia. There was, of course, no pulse in the dorsalis pedis nor in the posterior tibia artery at the ankle.

During the course of the next two months, extensor power of the foot began to return and the flexor power became increasingly strong. The sensory disturbance had also diminished and the Achilles jerk was more brisk.

Case 12.—The following case is one of injury to the posterior tibial nerve, the injury consisting of a division of a small portion with compression and atrophy of the nerve due to a dense cicatrix:

The patient was a young Servian officer, aged thirty-two years, of good physical makeup, wounded August 14, 1914. He came to France and entered the American Ambulance February 8, 1915. At that time, upon examination, the patient showed wounds in the left calf due, probably, to a rifle ball. The ball had entered the inner head of the gastrocnemius, 12 cm. below the internal condyle of the femur, passed posterior to the tibia and made its exit 22 cm. below the head of the fibula, fracturing the latter bone.

Immediately after the injury, patient experienced complete drop-foot. He fell from standing position, having considerable pain at the point of injury but none in the foot. The wound healed and the fracture united without complication, and after two months he was able to flex the foot on the leg.

Becoming impatient because of persistent pain upon resting his weight on the ball of the left foot he came to Paris and was sent to the American Ambulance. At the time of admission, five and a half months after date of injury, the right calf measured 32.5 cm., and the left 31.5 cm., an atrophy of 1 cm. There was a distinct flushed appearance of the left leg at the outer surface and an increased sense of warmth as compared with the right. There was slight edema of the left ankle and all movements of the foot were possible except flexion of the foot upon the leg, which was limited when a right angle was reached; in fact, it did not permit a passive movement beyond this point because of pain in the dorsum of the foot. Movement of the toes dorsally and in plantar direction was preserved. There was complete anesthesia upon the sole of the foot only to touch, pain, and temperature; pressure on the posterior tibial nerve produced the sensation of formication on the sole of the foot. The Archilles reflex was absent; there was no plantar response. Considerable pressure upon the plantar nerves and the posterior tibial nerve caused pain; pressure on the dorsum of the arch of the foot also produced pain.

The chief disability at that time, however, was pain in the ball of his left foot upon resting his weight upon it. The patient describes the pain as not especially situated in the sole, but rather inside the foot near the metacarpal arch.

Since there was no considerable motor disability the patient was placed upon massage and electricity, with a view to assisting recuperation of the injured nerve and to wait for complete reëstablishment of function. By the middle of April the Achilles jerk had returned, although the anesthesia remained the same. The skin of the sole was soft and glossy and desquamation was inclined to be delayed, and the sole of the foot began to show definite atrophy. The pain in the foot, though somewhat diminished, was still present and the patient limped about with a cane favoring this foot.

On May 27, 1915, Dr. Dubouchet exposed the posterior tibial nerve and found at the point of injury an hour-glass constriction of the nerve, due to original contusion and partial division, with subsequent dense cicatrix formation surrounding it, although a very small portion of the nerve had been cut. The nerve was freed from scar, a small neuroma trimmed away, and the freshened surfaces of the nerve were attached and the wound closed.

This patient was kept under observation for only two months following the operation, during which time no alteration in sensation had occurred. The pain in the foot was considerably relieved and the motor power remained as before the operation.

Case 13.—The following case represents a rather rare group of cases in which the small sciatic nerve was completely severed, and the great sciatic nerve contused.

The patient was a captain of infantry, aged thirty-six years, who was wounded, November 6, 1914, and arrived at the Ambulance on November 8. A rifle ball had entered the right thigh on the inner aspect in the upper third and had traversed the thigh and buttock, making its exit on the outer side of the buttock, having passed posterior to the femur and touched the posterior surface of the great sciatic nerve en route. At the instant of injury he was kneeling; he felt an instantaneous severe pain in the sole of the foot, which had not ceased at the time of admission. He was carried immediately on a stretcher to a poste de secour, where he was given first aid. He was then brought by train and ambulance to the hospital. He had had repeated injections of morphin without abatement of the pain.

Although the wound was apparently clean the unmitigating pain justified an operation, which was performed on November 10. Previous to the operation the patient lay in bed with the right leg flexed as the position of greatest ease. The right knee-jerk was greater than the left but the right ankle jerk was absent. The great sciatic nerve and all its branches and the muscles of the calf were extremely tender on pressure; even touch on the sole of the foot was so painful that he could not bear contact with the bed or bedclothes. The spontaneous pain was referred to the foot and the flexus of the knee. Movements of the leg and foot were possible, but that of the toes was very feeble. Over the posterior surface of the thigh was an elongated oval area of anesthesia to touch, pain, and temperature, extending from the great sciatic notch down to about 10 cm. above the flexus of the knee.

At the operation the great sciatic was exposed just below the notch where it makes its exit from the pelvis. The nerve was found to be intact; the small sciatic, however, was severed. The track of the bullet showed that it had passed across the great sciatic nerve without great damage. There was rather a marked inflammatory process surrounding the nerve, but no gross alteration in the appearance of the nerve itself was perceptible. The wound was kept open and allowed to heal by granulation. The patient experienced little relief following the operation, but great relief was derived from elevation of the foot and leg and exposure of the wound to the rays of an electric bulb several hours a day. Sodium bromide was also used efficiently. The improvement was gradual but certain, both in the disappearance of pain and the ability to move the leg and toes, so that by January 11, 1915, two months after the injury, the patient was able to walk with crutches. He could not, at this time, bear his weight upon the foot; in fact, did not use it in walking. It was not until two months later that he could bear his weight with any degree of comfort. At this time, March 5, 1915, the scar of operation, 12 cm. long, running parallel with the thigh and between the tuberosity of the ischium and the great trochanter, had become insensitive. There was atrophy of the right thigh and leg, the right thigh measuring 38 cm. and the left 43 cm., 22 cm. above the patella. The circumference of the right calf was 25 cm.; of the left 29 cm., 13 cm. below the patella. There was weakness in flexion of the leg and in both flexion and extension of the foot. The sciatic nerve, posterior tibial, and the plantar were moderately tender on pressure, especially the latter. Pressure upon the centre of the scar produced pain in the foot.

It was not until April, 1915, six months after the injury, that the patient was able to walk alone and with a normal gait. The atrophy persisted but the tenderness had practically disappeared.

Case 14.—This case represents an uncommon group in which injury to the long or internal saphenous was the isolated neurological finding.

The patient was a recent graduate of medicine, aged twenty-eight years, engaged with his company as a surgeon at the time he received his wound. He was wounded October 28, 1914, and arrived at the hospital October 31. His wounds consisted of small pieces of shell which had peppered the right thigh in its upper portion; one small piece had entered the knee joint. When wounded he was walking beside a stretcher upon which a wounded man was being carried by four others. A shell exploded about three meters in front of them, killing the wounded man and the four carriers and wounding the patient, knocking him off his feet. He got up, felt short of breath, felt blood trickling down the right leg of his trousers, and thought from the position of the holes in his trousers, that his femoral artery might have been injured. Grasping the artery in the groin he walked 15 meters to the poste de secour. When he arrived he felt faint and lay down. He then began to experience a lancinating and burning pain down the right leg and at the same time a dead feeling in the foot. His wounds were dressed and pronounced not serious, and he was sent by train and ambulance to the hospital.

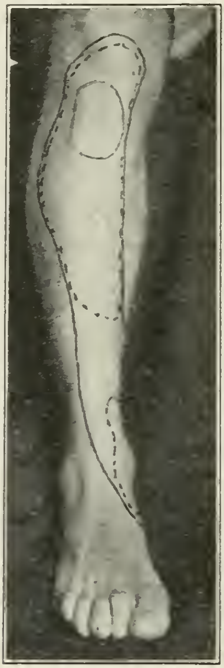

FIG. 9.—Case 14. Injury to the long saphenous nerve. Within the area anesthetic to light touch were areas upon which brushing the finger caused "burning." The small oval area was completely anesthetic.

The operation, November 1, consisted in removing the various pieces of shell which had imbedded themselves in the quadriceps muscle. No attempt was made to remove the fragment in the knee.

I saw him first a week later, when he complained of hyperesthesia over the foot and leg, even to the touch of the sheet, and as for wearing his sock, it was impossible.

Upon careful examination it was discovered that to the light touch of cotton wool or a camel's hair brush there was a strip of anesthesia 10 cm. wide, beginning at the middle of the patella, passing down the front of the shin and turning off to include the inner surface of the foot and ankle. Within this area were two areas which produced a burning sensation when the finger was rubbed over them or a pin dragged across them. These areas are represented as included within the dotted lines of the photograph. Just below the patella, within the area paresthetic to the pin scratch, was a small oval area of anesthesia. There was a small strip about 1 to 2 cm. wide on either side of the area anesthetic to touch which gave a burning sensation when pricked with a pin. Light pressure upon one of the small scars, of which there were five or six, in the middle of the thigh caused a tingling through the anesthetic area.

The hyperesthesia gradually subsided, so that by December 1 his wounds had healed and he was able to wear his sock and shoe without discomfort. His chief complaint was, and continued to be, the slight disability from the morsel of steel remaining in the knee-joint, probably in the cartilaginous portion of the end of the femur. This disability gradually improved without removal of the fragment.

The anesthesia described over the leg persisted as well as the areas yielding a burning sensation upon a pin scratch; in fact, they were present at the time I last saw him, April 12, 1915, six and a half months after the date of his wounds.

The distribution of his neurological disturbance pointed to a severe injury to the long saphenous nerve, which doubtless occurred near its origin high up in the thigh. It was not observed on operation, but the lack of improvement in regard to the anesthetic and paresthetic symptoms would indicate that it was almost severed.

Case 15.—This case represents a group in which the injury involved the entire brachial plexus.

The patient was a young officer, aged thirty-two years, wounded October 19, 1914, while lying on the ground, firing. A rifle bullet entered the muscles of the shoulder posteriorly and below the spine of the scapula and passed upward into the shoulder, carrying with it pieces of a pair of field glasses, including the leather case and parts of the buckle on the case.

The patient was in instant agonizing pain and thought that his right arm had been shot off near the shoulder. He looked at his arm and hand, and finding them attached to his body, attempted to move them but was unable.

The patient entered the hospital October 22. A roentgen-ray examination showed various fragments of foreign bodies in the shoulder and axilla beneath the joint. The wounds were badly infected and were opened for drainage. Finally, on November 12, Dr. Dubouchet removed the lead portion of the bullet above the clavicle and the jacket of the bullet was removed from the chest wall. A piece of leather from the case escaped from the sloughing wound some weeks later, as did also small pieces of the buckle.

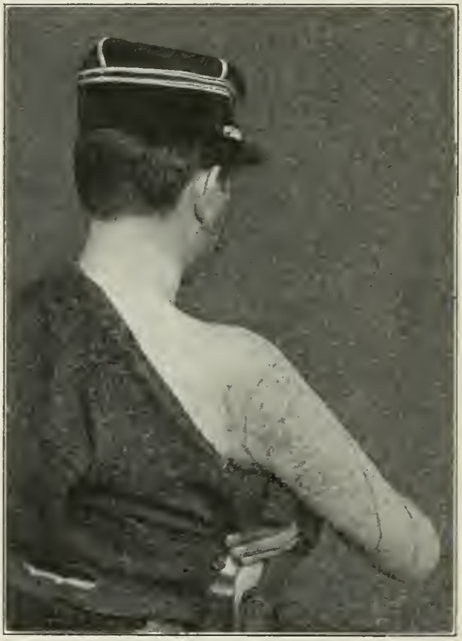

FIG. 10.—Case 15. Contusion of the brachial plexus. Note atrophy of the shoulder and arm muscles. Note particularly the dystrophic patchy desquamation.

During November any passive movement of the fingers, hand and arm was associated with great pain; no active movement was possible. There was about 1 cm. of atrophy in the arm and 5 cm. in the forearm, and interosseal atrophy in the hand.

During December feeble flexion of the arm appeared, but there was still none at the wrist and very little of the fingers and thumb. Abduction and adduction of the fingers was weak and no extensor power of the hand was possible. There was no deltoid action. There was hypesthesia of the entire arm below the shoulder. The triceps reflex was absent but the biceps was present.

During January, the third month, improvement proceeded rapidly. The flexor power returned more rapidly than the extensor power in the forearm, wrist, and fingers. During this period he was receiving passive movements, massage, and electrical treatments.

By the beginning of February the extreme sensitiveness to touch had disappeared, and flexion of the wrist and fingers was complete but weak. Opponens power and adduction were feeble; there was slight extension of the wrist, better in the fingers but not complete in either. Complete flexion of the forearm was possible and the biceps reflex was very active. Extension of the forearm was incomplete and the triceps reflex absent. The deltoid contracted slowly, but he could not raise the arm more than 45 degrees. The skin of the fingers was smooth and glossy, and there was a pronounced tapering of the fingers as compared with the other hand. There was partial obliteration of the wrinkles at the joints. The palmar surface was moist and of a deep pink color. The nails are long, narrow and curved. The desquamation over the posterior surface of the arm was peculiarly faulty. Large and small pale brownish or yellowish plaques of epithelium adhered to this area. Over this area, where desquamation was most faulty, there was anesthesia to touch, pain, and temperature, as indicated in Fig. 10. There was diminished sensation over the hand except the tips of the fingers, which were hypersensitive.

During the succeeding five months the motor power gradually returned to the hand and arm; the feeblest and weakest movement being the elevation of the shoulder, which was not complete, nor did the anesthetic area disappear. There was still slight atrophy of the arm and forearm and of the muscles of the shoulder tip of the scapula. The sensitiveness of the skin had entirely disappeared. The hand grasp was firm but not powerful.

It was, therefore, at least nine months before the contusion of the plexus at the shoulder recovered, and then not completely, as there was still disability in the circumflex, and general weakness in the arm and hand.

Case 16.—I will now pass to an interesting case of injury to the lumbo-sacral plexus. The majority of cases of injury to the sacral plexus usually involve the pelvis and the peritoneum to such an extent that the patient was in too critical a condition to examine or in such great pain that the findings were not reliable.

This case was one of a young lieutenant, wounded at Florence, August 24, 1914. While sitting his horse a shell exploded about 2 meters behind him and near the ground. A large flattened piece of shell, about the size of the hand, passed completely through the body of the horse, severing its vertebral column just behind the saddle and striking the rider upon a pair of field glasses which hung from his shoulder, flattening the latter to the thickness of a hand against the upper pelvic and lower lumbar region of the left side, and together with the force of the explosion knocked the rider over the head of the mortally wounded animal. He was able, with the aid of two men, to get upon his feet and experienced great pain in his left thigh, leg, and foot as well as in the left lumbar region. He lay two days in a box car, the pain being greater lying than when sitting. Finding himself unwounded, except for a bruise where the field glasses had hung, he returned to duty the third day, in spite of his pain, and was with his company sixteen days when his horse slipped and both went down, the man striking his left side. He got up and walked, with great pain in the left lumbar region.

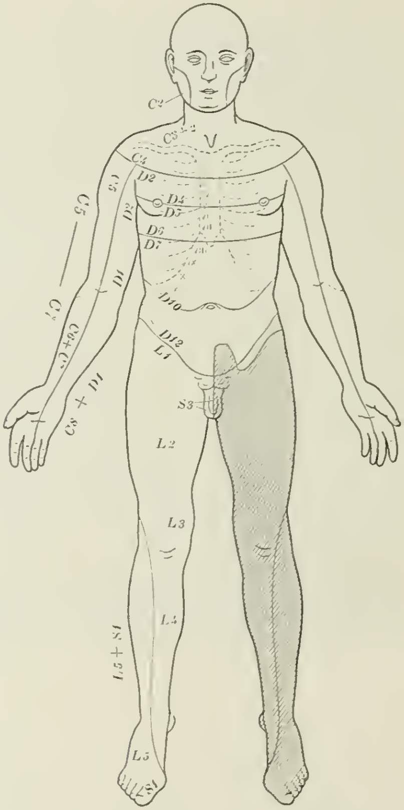

FIG. 11.—Case 16. Contusion of the left lumbo-sacral plexus. The hatched area was markedly hypesthetic to touch, pain, and temperature. Note particularly the area supplied by the ilio-hypogastric nerve, showing that all nerves from the plexus were affected

He was taken to an improvised hospital, where he lay for one month. At the end of that time he attempted to walk and did so for two or three hours, following which the pain in the left loin and thigh became excruciating.

He entered the American Ambulance on November 13, 1914, and at that time he complained of severe pain in the left lumbar region and down the left lower extremity of the foot posteriorly and inability to walk because the slightest weight of his body upon his foot increased his pain.

He was a man aged thirty years, of large frame and very muscular. There was over the left sacral region posteriorly, the last remnant of a bruise. There was no evidence of atrophy in the left lower extremity, but even light pressure over the left lower abdomen or over the left lumbar region, or down the course of the sciatic, produced intense pain. Pressure at the anterioi iliac spine caused pain below the great trochanter. The crest of the ilium was very tender on pressure; even the slightest pressure on the sole of the foot was intolerable. There was no paralysis, but extreme movements of the lower extremity increased his pain. The knee and ankle reflexes were preserved. Over the entire extremity existed a diminished sensation to all modalities of stimulation, which amounted almost to anesthesia. This hypesthesia extended anteriorly up to the groin, latterly, and toward the median line, extended upon the abdomen about 4 cm., halfway to the umbilicus. The hypesthesia also obtained over the left half of the penis and scrotum, posteriorly the hypesthesia extended up over the hip as far as the level of the top of the sacrum.

During the next month there was a slow return of acuteness of sensation throughout the extremity and a partial disappearance of tenderness of the lumbar region, but the sciatic and its branches remained very sensitive to pressure, and pain on movement of the hip remained. He was able to move the knee and foot without pain.

On December 12, 1914, his pelvis and lumbar region were immobilized by a plaster cast extending over the short ribs to the upper thighs. During the next six weeks the pain gradually disappeared, and sensation became completely reëstablished. A week later he was fit for discharge and went home walking with crutches, as there was still some tenderness when his weight was permitted to rest on his left foot. The left sacro-iliac joint was still tender to pressure.

The following conclusions may be drawn concerning injuries to peripheral nerves produced by shot and shell:

1. Laceration and contusion may be differentiated usually by careful neurological examination. In some cases exposure of the nerve at the site of the injury is the only means by which exact knowledge of the nature of the injury to the nerve is obtained. Neither test of function nor electrical reaction will differentiate contusion from laceration.

2. Cases of simple contusion recover slowly, and as a rule completely.

3. Gunshot and shell wounds causing lacerations of the nerves do not lend themselves readily to plastic operations. Because of the infection weeks and months elapse before plastic work can be undertaken. During ten months no recovery in such cases was observed.

THE DIETETIC MANAGEMENT OF HYPERCHOLESTERINEMIA IN CASES OF CHOLELITHIASIS.

By M. A. Rothschild, M.D.,

and

N. Rosenthal, M.D.,

new york.

(From the Pathological Laboratory, Mount Sinai Hospital, New York City.)

The relationship of cholesterin to gall-stone formation has been emphasized by many authors. Naunyn[1] has claimed that cholesterin is an excretory product of the epithelium of the gall-bladder and bile ducts. Aschoff and Bacmeister[2] have conclusively shown that when cholesterin is found in the epithelium of the gall-bladder it is due to resorption from a saturated bile. Aschoff has especially emphasized the mechanical conditions in the gall-bladder and ducts as the important factor in the formation of precipitation stones which consist practically of pure cholesterin. Chauffard[3] and Bacmeister and Havers[4] have called attention to the relationship of hypercholesterinemia to the formation of gall-stones. In pregnancy we have a physiological hypercholesterinemia, and it has been well established that gall-stone formation is more frequent in pregnant women. Bacmeister and Havers have shown in their work on a pregnant dog with a biliary fistula that there is a real retention of lipoids in pregnancy. With the birth of the young there is a sudden excretion of the retined lipoids. This would naturally lead to an excretion of a bile more or less saturated with cholesterin with a resulting tendency to the formation of pure cholesterin stones. The gross and microscopic appearance of these stones lends strong support to this view. The physical characteristics of these precipitation stones show that they are composed of a conglomerate mass of cholesterin and are not formed by a gradual deposit in concentric layers, demonstrating that there is a more or less sudden precipitation of cholesterin from the bile in the gall-bladder and ducts.

One of us[5] has recently shown that the cholesterin content of the blood and bile depends upon the type of food the organism consumes. Herbivora ingest relatively small quantities of cholesterin, and consequently show relatively small quantities in their blood and bile; whereas the diet of carnivora and omnivora is richer in cholesterin and the blood and bile contain correspondingly higher quantities of cholesterin.

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[1] Klinik der Cholelithiasis, Leipzig, 1892. München. med. Wchnschr., 1898, xiv, 1293.

[2] Cholelithiasis, Jena, 1909.

[3] Leçons sur la Lithiase Biliaire, Paris, 1914.

[4] Deutsch. med. Wchnschr., 1913, No. 8.

[5] Rothschild, Ziegler's Beitr., 1914, lx, 39, 66 and 227; Proc. New York Path. Soc., 1914, xiv, 159, 229.

The complete cholesterin metabolism was outlined by one of us as follows: "There is no synthesis of cholesterin in the body. Our supply of lipoids is maintained by our food intake. Free cholesterin is esterized in the intestinal canal, absorbed by the lymphatics, delivered to the blood stream and then distributed to the body cells. With the breaking down of cells, as in general catabolic processes, it is again freed to the blood stream, carried to the liver, where the endothelial cells possibly produce a deësterization (an intermediary part), excreted with the bile as free cholesterin and again partially reësterized and reabsorbed from the intestinal tract by means of the lymphatics."

It was also demonstrated chemically that in experimental hypercholesterinemic states the blood shows a normal cholesterin content before the cholesterin content of the liver returns to normal. In other words, in an animal made hypercholesterinemic by feeding pure cholesterin, the cholesterin in the blood on stoppage of the feeding, gradually returns to its normal figure, the bile still showing an increase and the liver chemically an excess. At a little later period this excess in the liver is excreted until the cholesterin content of the bile returns to normal. Chalatow[6] has produced small concrements in the gall-bladders of rabbits by feeding large quantities of cholesterin. He also demonstrated that these concrements consisted of practically pure cholesterin.

Henes[7] has claimed that a hypercholesterinemia may be used as one of the differential points in diagnosing cholelithiasis from other abdominal conditions, especially gastric ulcer, in which the cholesterinemia is either normal or subnormal. This statement has, in fact, many elements of truth, but the exceptions are manifold. In five cases of gastric or duodenal ulcer the cholesterin content of the blood was determined and gave the following figures:

0.097 per cent.	0.166 per cent.	0.248 per cent.
0.155 "	0.237 "	

It is evident from these results that the cholesterin content of the blood may be very variable in this condition. Concomitant pathological or physiological factors that may cause a hypercholesterinemia must be considered in each case. For example, in atherosclerosis or chronic nephritis we find a hypercholesterinemia even though an ulcer be present. Similarly, patients with pyloric obstruction or repeated vomiting or those in a state of inanition may show a transient hypercholesterinemia even in the presence of an ulcer.

Conversely, all cases of cholelithiasis do not show a hypercholesterinemia. Thirty-seven cases examined by the authors gave the following figures:

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[6] Ziegler's Beitr., 1913, lvii, 85.

[7] Jour. Am. Med. Assn., 1914, lxiii, 146.

0.425 per cent.
0.350 "
0.330 "
0.325 "
0.290 "
0.287 "
0.281 "
0.275 "
0.272 "
0.250 "
0.237 per cent.
0.237 "
0.235 "
0.218 "
0.215 "
0.212 "
0.212 "
0.2115 "
0.207 "
0.205 per cent.
0.205 "
0.200 "
0.200 "
0.200 "
0.190 "
0.175 "
0.170 "
0.166 "
0.162 per cent.
0.162 "
0.160 "
0.150 "
0.150 "
0.145 "
0.135 "
0.132 "
0.132 "

The highest hypercholesterinemia was found in cases that were jaundiced. In general, it may be stated that cases of cholelithiasis do show a hypercholesterinemia. However, in 12 cases there was a normal cholesterin content of the blood, yet gall-stones were demonstrated at operation. The explanation of this group evidently lies in the fact that at some previous period a hypercholesterinemia was present, as precipitation stones were found in the gall-bladder which automatically reduced the hypercholesterinemia. Unless the same physiological and pathological factors that originally caused the hypercholesterinemia persist after the formation of the stones or unless obstruction results from the stone formation, the hypercholesterinemia will not reappear. A simple obstruction of the cystic duct will not produce a hypercholesterinemia. The presence of infection will reduce the cholesterin content of the blood even in cases of cholelithiasis. In three such cases an empyema of the gall-bladder was noted and in two of them the cholesterin content of the blood was 0.132, 0.135 and in the third 0.175 per cent.

We have observed cases in which the gall-bladder had been removed and in some of which the common bile duct had been drained, and despite the removal of the gall-bladder, thus theoretically reducing the chances of stagnation in this organ, a hypercholesterinemia persisted not assignable to any determinable cause.

This has led us to divide our cases of cholelithiasis into the following groups:

Group I. Cases that have a normal cholesterin content of the blood.

Group II. Cases that are hypercholesterinemic. The hypercholesterinemic cases are in turn divided into the following groups:

- A. Obstructive hypercholesterinemia
    - Temporary
        - Stone.
        - Stricture.
        - New growth, etc.
- B. Diathetic hypercholesterinemia
    - With obstruction.
    - Without obstruction
        - Intermittent.
        - Permanent.

We shall not enter into a lengthy discussion of Group I. In this group are included stone cases which subsequently may be placed in Group II. As an example, a patient with an empyema of the gall-bladder may be hypocholesterinemic because of the infection but with the removal of the gall-bladder and the subsidence of the infection a condition of hypercholesterinemia may be established and the case would then belong in Group II.

The obstructive hypercholesterinemias in Group II are called temporary, as with the removal of the obstruction the hypercholesterinemia disappears. For instance, a patient with an afebrile obstructive jaundice is hypercholesterinemic. With the removal of the obstruction the cause of the hypercholesterinemia is likewise removed, the cholesterin content of the blood returns to normal and the patient then belongs to Group I.

There is, however, in Group II a second class of patients who are more or less continuously hypercholesterinemic. These we have called the diathetic group, or those having a cholesterin diathesis. We do not wish to report these cases in detail until we have observed them over much longer periods. At present we wish only to point out the general principles involved.[8] A typical case of this group will serve as an example:

Case History.—A woman, aged thirty years, had a cholescystectomy performed one year ago for cholelithiasis. The common bile duct was drained. She remained free of symptoms for two months, when the symptoms returned. There were mild attacks of pain in the right upper abdominal quadrant. These pains occasionally radiated to the back and shoulder. Associated with the attacks there was nausea, sour eructations, and occasionally vomiting. The duration of the symptoms was usually from twenty-four to seventy-two hours. No elevation of temperature was ever noted. The attacks increased in frequency and were accompanied by slight jaundice, which disappeared in the free intervals. The frequency of the attacks and the more frequent recurrence of jaundice caused the patient to seek surgical interference. Upon operation a dilated common duct was found containing soft, yellowish-black débris with a few small rounded stones. The common bile duct was drained for several days, the tube eventually removed and the fistula allowed to heal.

Numerous studies were made by us upon patients of this diathetic group. We have thus far observed nine individuals belonging to this group. After cholecystectomy these patients remain free of symptoms for three months to one year. Six of the nine patients again sought surgical relief within seven months to three years after the primary operation. Three patients with definite symptoms at present have not yet submitted to a secondary operation. Examination of the blood in these nine cases shows that they all are hypercholesterinemic; the cholesterin content of the bloods being as follows:

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[8] Studies on this group will be reported later.

0.350 per cent.	0.281 per cent.	0.272 per cent.
0.330 "	0.280 "	0.237 "
0.325 "	0.275 "	0.218 "

We have further divided this group into cases with obstruction and cases without obstruction. In those with obstruction, the removal of the obstruction should remove the cause of the hypercholesterinemia as in Group A. If after removal of the obstruction, however, the patients remain persistently hypercholesterinemic, they then belong to Group B, the diathetic group. In the cases without obstruction we have again two classes: those with intermittent hypercholesterinemia and those with permanent hypercholesterinemia. As an example of the intermittent type the following may be cited: A patient with gradually progressing hypercholesterinemia develops a mild or severe attack of cholelithiasis. The precipitation of the retained lipoids in the gall-bladder or bile ducts in the form of cholesterin stones or cholesteatomatous material with or without subsequent expulsion automatically diminishes the cholesterin content of the blood. Because of the diathesis, however, the cholesterinemia again increases until once more relieved by lipoid precipitation. The permanent hypercholesterinemias are of similar nature, but in them the cholesterin content of the blood at no time returns to normal values.

The question naturally arises, Why are the cases in this diathetic group hypercholesterinemic? In an attempt to determine this point we have carried out systematic studies on this group as follows: The cholesterin content of the blood was determined before operation and at frequent intervals both during and after the drainage period. Cholesterin determinations were also made in the bile in twenty-four hour specimens. Lastly, the stones removed at operation were quantitatively analyzed. The patients reported to us at regular intervals for cholesterin determinations of the blood while under dietary control, even after they left the hospital.

Mrs. M. Dr. J. C. A. Gerster. Primary operation, cholecystectomy.

Second operation, February 18, 1915, choledochotomy. The common bile duct was found to contain fairly large quantities of yellowish-black granular material with a few small yellowish rounded stones. Chemical examination of these stones and the granular material demonstrated that they consisted of practically pure cholesterin mixed with small quantities of bile pigments.

Date.	Blood. Cholesterin content. %	Bile. Quantity. c.c.	Cholesterin content. %
Feb. 18	0.280	220	0.07
19	...	150	0.110
21	0.103		
22	...	110	0.09
23	0.155	56	0.087
24	...	200	0.12
25	...	450	0.132
26	...	420	0.075
27	...	360	0.068
29	0.095		
Mar. 10	0.130		
April 22	0.162		
May 5	0.187		
20	0.178		
June 4	0.155		
Sept. 16	0.168		

This case was chosen as an example, as it is the case we have observed over the longest period. The blood was obtained only upon the day following operation. It is reasonable to suppose that if we had obtained the blood previous to the operation, the cholesterin content would have been higher, as anesthesia, the elevation of temperature, and drainage of the common bile duct may all be regarded as factors tending to diminish the cholesterinemia. An analysis of these figures shows the following important points:

1. The patient is hypercholesterinemic at the time of operation (0.280 per cent.).
2. The material found in the bile ducts is practically pure cholesterin admixed with some bile pigments.
3. With the loss of most of the bile, and the consequent prevention of reabsorption from the intestinal tract, the content of the blood in cholesterin falls below normal (0.103 per cent.).
4. With the removal of the drainage tube (on February 29) the blood begins to reach normal figures (0.130 per cent.).
5. With unrestricted diet until May 5 a slight hypercholesterinemia is again present (0.187 per cent.).
6. From May until September the cholesterin content of the blood is kept within normal limits by purely dietetic measures.

Analyzing the above figures more closely we develop the following facts as well: The hypercholesterinemia was relieved before the cholesterin content of the bile returned to normal. The drainage tube became plugged on the 22d, and less bile was drained, only 56 c.c. Thus more bile reached the duodenum, and as a result the blood promptly rose from 0.103 to 0.155 per cent. When drainage was reëstablished the cholesterin content of the blood again fell below normal. The character of the bile drained during the first few days gives interesting confirmatory evidence. It contained much granular débris consisting of cholesteatomatous material. The physical characteristics of the bile became normal on the 25th. The patient was practically on a cholesterin-free diet until the 23d, during which period large quantities of retained lipoids were excreted. After this period the patient was allowed an ordinary hospital diet containing rather large quantities of lipoids, and the cholesterin content of the bile increased. The diet was again changed, so that practically no cholesterin was ingested, and the cholesterin content of the bile fell to normal figures. From February 29 to March 5, even though the drainage tube had been removed, there was considerable escape of bile from the incompletely closed fistula which served to maintain the cholesterin content of the blood at a low figure. On March 10 the fistula was almost closed and the cholesterin content of the blood promptly rose to normal. From this time on a restricted diet free from lipoid-rich foods the blood cholesterin remained within normal limits.

We feel that we have demonstrated a definite relationship between hypercholesterinemia, the character of the stones in the bile ducts, and the physiology of the operative procedures used in helping these patients. The drainage of the bile ducts reduced the hypercholesterinemia and drains the liver of the excess of retained lipoids. These patients are thus relieved until a reaccumulation of cholesterin takes place. It is evidently not feasible to repeatedly drain the common bile ducts; hence other methods of treatment were investigated. The natural question which arises is, why are these people continuously hypercholesterinemic? We cannot explain this phenomenon on an obstructive basis alone, as hypercholesterinemia is found in this diathetic group even in the absence of obstruction. Where obstruction due to precipitated material does occur chemical examination proves the nature of the obstructing substance to be cholesterin.

The following question also suggests itself: What is the source of the cholesterin, and why do not these individuals excrete it as does the normal person? One of us has shown that the only source of cholesterin is the food intake and the bile is the only medium of excretion for the absorbed lipoids. Careful investigation of the diets of these patients reveals no conclusive facts. They eat practically the same kinds of food as the normal individual. We must presuppose some inherent physiological weakness or diathesis to explain the retention of cholesterin. Exactly as some individuals have a so-called gouty or uric acid diathesis with a retention of uric acid, these individuals retain their lipoids. That is, there is a retention hypercholesterinemia, the excretion of a more or less saturated bile, and ultimate precipitation of the retained cholesterin in the gall-bladder, the common duct and its finer radicals. The subsidence of an attack means that the patient has rid himself of the obstruction and will be in good health until the saturation point in the blood and bile is again reached. We have no evidence that this is due to some disturbance in the liver, as in hepatic disease such as cirrhosis and acute atrophy we have constantly found a hypocholesterinemia and not a hypercholesterinemia. We wish to point out that this is a real diathesis, and that only in this type of individuals do we get the previously described train of symptoms. This diathesis undoubtedly has a definite etiological relationship to other conditions which we are investigating (atherosclerosis, etc.).

The recognition of this diathesis is extremely important for the patient. We feel that under proper dietetic management in a large percentage of these cases a secondary operation might be avoided. One should examine the blood of every case of cholelithiasis without jaundice for cholesterin before operation. If the patient has a hypercholesterinemia, he probably belongs to Group II. In the presence of hypercholesterinemia, provision should be made for drainage of the bile to deplete the body of the retained lipoids. The drainage tube should not be removed until the blood and bile show a normal cholesterin content, and during this period the diet should be low in lipoids. After removal of the drainage tube and the closure of the fistula the blood should again be examined, and if the cholesterin content is high the patient definitely belongs to Group II.

Further accumulation of cholesterin can be controlled by dietetic measures. The principles of dietetic management are based on the following experimental facts: It is extremely difficult to cause a hypercholesterinemia in a dog by feeding pure cholesterin, as the excess is rapidly excreted through the bile. It was thought that by tying the common bile duct and then feeding pure cholesterin an extreme grade of rapidly developing hypercholesterinemia would result. However, no greater hypercholesterinemia developed than is explainable by the obstruction of the common duct due to the ligature. In other words, free cholesterin as such in the absence of bile is not absorbed from the intestine. To the same dog free cholesterin plus bile from another dog was fed and a slightly greater absorption resulted. Free cholesterin plus bile and fat were fed simultaneously and still greater absorption was demonstrated. The feeding of these substances in combination practically amounted to feeding cholesterin esters, and subsequently when cholesterin esters were fed, the maximum amount of absorption resulted.

Using these facts as a basis of dietetic treatment, we believe first that since the cholesterin content of the blood is dependent upon the cholesterin content of the food, by diminishing the latter, we can correspondingly diminish the former; and second, that by rendering the absorption of cholesterin as difficult as possible, the cholesterin content of the blood will also be lowered. These two conditions can be satisfied by placing the patient on a fat-free diet which both excludes lipoids to a large extent and renders difficult the esterization of the free cholesterin in the food.

Our foods in general are poor in cholesterin esters. Those articles of diet which are rich in lipoids are excluded—eggs, cream, butter, meat, and fish. On a strict practically lipoid-free diet, only vegetables are allowed, excluding beans and peas which are fairly rich in a metameric product, phylocholesterin. All other vegetables, as well as cereals and sugars, are allowed. The milk should be skimmed and fat-free buttermilk permitted. This diet is so strict that the majority of patients will not maintain it for a long period; therefore we have devised "fast and feast day" periods. For three or four days a week the patient lives on the strict, lipoid-free diet outlined above, the so-called fasting periods, which serves to deplete the organism of the stored-up lipoids. For the next three or four days, dependent upon the grade of the hypercholesterinemia, a more liberal diet is permitted, the so-called "feast days." On the "feast days" the patient is allowed, in addition to the articles stated above, well-cooked lean meats and fish, excluding salmon, shad, and bluefish, the fat content of which is high. Oleomargarin is allowed instead of butter. On this regime we have controlled and reduced the lipoid content of the blood of our series of cases. In one case the hypercholesterinemia which was 0.330 per cent. (normal 0.160 to 0.180 per cent.) was reduced to 0.233 per cent. in fourteen days; in another from 0.350 to 0.268 per cent. in ten days. In four other cases the cholesterin content of the blood has been maintained at the normal figure since operation, a period of two to eight months. The first two cases cited above have not as yet required a secondary operation. Our other cases are too recent to determine the permanent effect of dietetic treatment and will be reported after a longer period has elapsed.

Three cases were not treated dietetically. One had a cholesterin content of the blood of 0.200 per cent. on January 22, 1915, which fell after drainage for four days to 0.125 per cent., but again rose to 0.195 per cent. on July 18. The second case had before operation a hypercholesterinemia of 0.250 per cent., which after drainage for eight days fell to 0.166 per cent. but seven weeks later again rose to 0.210 per cent. A third case at the time of operation had a hypercholesterinemia of 0.275 per cent. and three months later a hypercholesterinemia of 0.245 per cent. These cases we are at present using as controls to determine whether or not they will develop symptoms in contradistinction to those cases treated dietetically.

For the present we simply wish to point out the results of our studies in these groups of cases and to especially emphasize the fact that there is one group of cases which, despite the removal of the gall-bladder or the removal of any cause for an obstructive hypercholesterinemia, remains or soon becomes hypercholesterinemic. These cases are frequently submitted to secondary operations with only temporary relief of symptoms. We have also shown that adequate drainage of the bile reduces this hypercholesterinemia, and that these patients, if promptly put upon properly selected diet, will not develop a hypercholesterinemia. Whether or not they may develop subsequent symptoms we must at present leave open until we have observed our cases for a longer period of time. However, we feel that if the hypercholesterinemia can be controlled we will have solved at least one of the important etiological factors in these individuals suffering from chronic cholelithiasis.

INFLUENZAL MENINGITIS, WITH REPORT OF A CASE.[1]

By Robert G. Torrey, M.D.,
PHILADELPHIA, PA.

Cerebrospinal meningitis caused by the influenzal bacillus is reported not infrequently, and probably often occurs without recognition, as there is nothing in the course or symptomatology of this disease to distinguish it from meningitis due to other acute infections. The only means of diagnosis is a careful bacteriological examination of the spinal fluid.

In 1911 Flexner[2] published a summary of the information possessed regarding this condition up to that date, and earlier in the same year Wollstein[3] reviewed this subject thoroughly, collecting 49 cases from which the influenza bacillus was recovered in pure culture and 9 in which it occurred with other organisms. Simon,[4] at about the same time, reported 2 cases and collected 41, including 12 not in Wollstein's series. These two series combined gave a total of 61 cases of pure infection and 9 of mixed, with only five recoveries. Since that time I have noted reports of 26 additional cases with two recoveries. A review of these reports tends to confirm previous figures regarding the high mortality of the disease. Including my own case, 89 cases show only eight recoveries.

Wollstein seems to have made a real advance in the specific treatment of this infection. A serum was prepared by immunizing a goat by means of virulent strains of the influenza bacillus, and with this serum she was able to successfully control experimental influenzal meningitis in monkeys.[5] The disease was rapidly and invariably fatal in the untreated animals, but complete recovery without complications was obtained by the intra-dural injection of serum.

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[1] Read before the Section on Internal Medicine of the College of Physicians of Philadelphia, January, 1916.

[2] Jour. Am. Med. Assn., vii, No. 1, 16.

[3] Am. Jour. Dis. of Children, 1911, 1, 42.

[4] Monatschrifte f. Kinderheilk., 1910, 9, 549, orig.

[5] Wollstein, Jour. Exp. Med., 1911, xiv, 73.

The case reports published since Wollstein's paper appeared include the following:

1. Hymanson. *New York Med. Jour.*, December 5, 1909. Age, six and a half months. Fatal. Ill three weeks.
2. Age, eight months. Fatal. Ill ten days.
3. Brem and Zeiler. *Am. Jour. Dis. of Children.* 1911, l, 417. Age, eighteen months. Fatal.
4. Age, twenty-three months. Fatal.
5. Clemens and Gould. *Arch. Ped.*, 1911. Age, seven months. Fatal. Ill eight days.
6. Rhea. *Arch. Int. Med.*, 1911, viii, 132. Age, six months. Fatal. Ill four days.
7. Age, five years. Fatal. Ill eighty-nine days. (Internal hydrocephalus.)
8. Klinger. *Correspond.-Blatt. f. Schweiz. Aertz.*, 1912, 1289. Age, two years. Fatal.
9. Age, five years. Fatal.
10. Age, five years. Fatal.
11. Age, twenty-six years. Recovery.
12. Jündell. *Hygiea,* Stockholm, 1912, lxxiv, No. 3. Infant. Fatal.
13. Giese. *Ugesk. f. Laeger.*, 1913, xxv. Ref. *Jour. Am. Med. Assn.*, 1913, 1, 1675.
14. Ross and Moore. *Brit. Med. Jour.*, 1913, II, vol. 25. Age, thirteen months. Fatal. Five punctures.
15. Tebbut. *Med. Jour. Australia,* October 31, 1914. Age, eight months. Fatal. Ill thirteen days.
16. Grasty. *Am. Jour. Obst.*, lxvii, 1031. Age, two years. Fatal. Ill fifteen days.
17. Ely and Weingart. *Jour. Iowa State Med. Soc.*, 1915, v-x. Age, three and a half years. Fatal. Ill eighteen days.
18. Hill and Packard. *Lancet-Clinic,* 1915, xii, 723. Age, twenty-two years. Fatal. Ill sixteen days.
19. Age, two years. Fatal. Ill two weeks.
20. Age, five months. Fatal. Ill nineteen days.
21. Age, four months. Recovery. Ill thirteen days.
22. Age, five months. Fatal. Ill seven days.
23. Prasek and Zatelli. *Wien. klin. Wchnschr.*, xxiv, No. 26. Age, eighteen months. Fatal. Ill sixteen days.
24. Boland. *Lancet,* 1915, II, 704. Age, four months. Fatal. Ill fifteen days.
25. Ducrot. *Rev. méd. de la Franche comté.* Age thirty-two years. Fatal. Ill six days.
26. Imperatori. *Laryngoscope,* 1915, 580. Fatal. Ill twelve days.
27. Torrey. Age, eleven years. Recovery. Ill four weeks.
28. Age, eight months. Fatal. Ill seventeen days.

Herbert Henry[6] reports 9 cases of meningitis in which an influenza-like organism was recovered from the spinal fluid. In three of these cases the fluid was sent to his laboratory for examination, but he did not get reports on the clinical history of the patients. In 2 the culture died without sufficient study. Henry regards the organism as similar to, but distinct from, the true Pfeiffer bacillus, though from the description of the cultures and inoculation experiments it seems probable that he was dealing with the influenza bacillus.

Sayce[7] reports 7 similar cases of meningitis occurring in Melbourne from 1906 to 1910. One patient lived for six months; in all the others the duration of disease was under three weeks. The ages varied from five months to five years. One patient, aged four years, recovered; all the others died. Sayce was unable to say whether this organism was identical with the influenza bacillus, but, as in Henry's cases, the description makes it seem probable that these were cases of influenzal meningitis. Owing to the doubt expressed as to the identity of the organisms, these cases are not included in the above series.

My case was of particular interest in that it afforded an opportunity for the trial of Wollstein's serum, of which a supply was furnished through the kindness of the Rockefeller Institute.

Case I.—A girl, aged eleven years, of good development, in normal health, intelligent and bright, became ill on November 15, 1915. Showed fever, general muscular pains, chills, stuffy feeling in the head, and vomiting. She complained of a very severe headache localized over the left eye, and occasional nausea and vomiting. She showed a pulse of 120 and a temperature of 103°. Marked tenderness over the frontal sinus on the left. Lungs were normal. Reflexes normal. No stiffness of the neck.

November 16. Examined by Dr. Packard, who reported that he found the nose and ears normal, and could find no evidence of any pus collection in the sinuses. Tenderness over the sinus has now disappeared.

November 17. Seen by Dr. Stengel in consultation. There was stiffness of the legs and pain down the legs and marked rigidity of the neck. Kernig's sign present. Photophobia marked. Temperature continued from 102° to 104°. Mentality clear. Knee-jerks diminished. Spinal puncture showed fluid turbid and under increased pressure. The smear from this fluid showed the turbidity to be due to cells which were nearly all polymononuclear, and there were present great numbers of organisms both in the cells and free. Dr. Wolferth, who examined the specimen, stated that the organisms seen on the smear were probably meningococci, but that they were not typical, and that he could not make a certain diagnosis until he had cultered the fluid. About 30 to 40 c.c. of fluid was withdrawn and 15 c.c. of antimeningococcic serum introduced. There was a drop of temperature and marked relief from the subjective symptoms following the tapping, but the temperature rose again after a few hours. The stiffness of the neck increased and retraction of the head and arching of the back became very marked. The patient is now lying on the side with the head stiffly retracted, so that the back of the head lies almost against the spinal column. There is no paralysis of the arms, but movement of the legs caused a great deal of pain.

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[6] Jour. Path. and Bact., xvii. 174.

[7] Australian Med. Jour., 1911, xvi, 25.

November 18. The second injection of antimeningococcic serum was given today. The fluid was more turbid than at the first tapping, but the organisms were found to be largely intracellular. Hexamethylenamin, gr. x, every six hours.

November 20. Dr. Wolferth reported a pure culture of influenza bacillus, and a supply of anti-influenza serum was kindly forwarded from the Rockefeller Institute. There was very marked retraction of the head and stiffness of the back, and slight internal strabismus of the right eye. Diminished knee-jerks. Temperature from 102° to 104°. Pulse 108 to 120. Mentality clear. Considerable twitching, also hoarseness and great difficulty in swallowing. Thirty c.c. of fluid were withdrawn. Very turbid, organisms practically all intracellular. Fifteen c.c. of the serum introduced. There was very intense pain in the hip, thigh, and leg on the side which the patient lay. This seemed to be accompanied by muscular spasm, and was apparently agonizing in its intensity. After introducing the serum there was, as before, a prompt subsidence of the temperature and pulse, followed by a sharp febrile reaction which lasted a few hours and dropped again. The condition of the patient now seemed better than before, and the back was a little less rigid, the strabismus disappeared, photophobia less. Seen by Dr. Martin in consultation.

November 21. Less arching of the back, the neck retracted as before, considerable difficulty in swallowing, and some hoarseness. Patient seemed brighter than the day before. Slept at short intervals. Injected 15 c.c. anti-influenzal serum, after withdrawal of 35 c.c. very turbid fluid.

November 23. Lumbar puncture. Removal of 30 c.c. Very turbid. Injection of 15 c.c. of anti-influenzal serum. This injection caused extreme pain in the legs, as did the previous ones. Occasionally slightly delirious.

November 28. Temperature has ranged from 99° to 103.4°, with irregular course. The pulse, for the most part, below 100, and the patient, on the whole, has seemed very much better for the past few days. Sleeping well all night. Mentality clear. Spinal puncture was done today and 40 c.c. of fluid withdrawn.

December 1. Very irritable; exceedingly hungry all day. Neck more mobile, no pain. Pupils show prompt reaction, no strabismus.

Knee-jerks normal. Spinal fluid opalescent, less turbid than previous specimen, and fair amount of fibrin collected on standing. Organisms somewhat fewer yesterday, all intracellular. Pressure, 300 mm. Withdrawal of 35 c.c. fluid. Vertical and temporal headache, which quickly subsided. Pressure 180 mm. Patient looks much better than heretofore. Less irritable, and less nervous after tapping.

December 2. Temperature has been normal all the afternoon. Pulse regular; 88 to 96. Pressure, 300 mm. Took out 7 c.c. more after brief rest. Back less rigid, appetite good, still somewhat irritable, no pain. Spinal fluid shows slight opalescence; about the same as yesterday. Six rabbits injected day before yesterday, two controls with emulsion of bacilli, four animals with serum and emulsion. All are alive and apparently well.

December 3. Thirty-five c.c. withdrawn, pressure dropped from 28 to 14 cm. With the withdrawing of the final 5 c.c. pressure fell to 11 cm. The smears from this fluid showed few organisms, and they were contained in relatively few cells, *i. e.*, an occasional leukocyte was found which was full of organisms, but these were rare.

December 4. Withdrew about 35 c.c., slightly turbid. Smear showed no organisms. Pressure 26 cm., fell to 14.

December 5. Temperature normal; pulse 100 to 108; no tapping. No pain or headaches.

December 6. Temperature reached 102° last night; pulse 112. Slept soundly, but there was a good deal of twitching of the muscles during sleep. Today, seems very well, appetite good, pulse perfectly regular, no pain, neck still retracted. Did not tap.

December 17. Another puncture was done on December 8 on account of nervousness and irritability. Pressure was 26 cm., which was reduced to 13 cm. by withdrawal of 30 c.c. of fluid. Fluid showed very slight turbidity. No organisms found in the smear. Leukocytes and polynuclears about equal in number. Thereafter the temperature remained about normal, never reaching 99. On December 15 another puncture was done. Thirty c.c. of clear fluid withdrawn. The pressure fell from 17 to 8 cm. Fluid perfectly normal in appearance. Both of the specimens were negative to culture. All the previous ones were cultured and showed the influenza bacillus alone. After the last puncture there was a prompt clearing up of the nervousness and irritability.

Summary. This patient apparently had a severe attack of influenza with a frontal sinus infection, followed by typical cerebrospinal meningitis. The organism isolated from the case showed a low degree of pathogenicity when tested by injection into rabbits. The spine was tapped thirteen times, and the influenzal organism present up to the last two tappings. There was an improvement of the symptoms following each tapping, both when the serum was used and when it was not employed. The fluid was more turbid following the first injection of antimeningococcic serum. It remained turbid as the organisms became fewer. The organisms at first were to a certain extent extracellular, but after the first injection of serum, they were almost always within the cells. The temperature was irregular throughout, but it was noted that following each tapping or injection there was a rise in temperature for a few hours. The use of the influenza serum was discontinued because the patient seemed to be improving, and because of the pain occasioned by its injection. With the clearing up of the organisms in the fluid, the temperature remained at normal, and the stiffness of the neck, which was the last remaining symptom, gradually disappeared.

Recovery was apparently complete with no nervous symptoms remaining. The only signs of high-pressure noted were extreme restlessness and irritability, which cleared up promptly with the removal of from 25 to 40 c.c. of fluid.

Case II.—M. G., American; aged eight months. Admitted to University Hospital October 28, 1914. Service of Dr. Frazier. Referred to Dr. Griffith's service. Through their courtesy I am permitted to report this case.

History of stiffness of neck, lump on head, refusal to eat, and vomiting. Has had a cold since August, but was bright and active until two weeks ago. Since then he has been very quiet and has not taken his feedings well; cough has become worse, neck has been stiff, and he has been feverish. Two weeks ago the mother noticed lump on his head, and for two weeks he has had attacks of vomiting.

Examination shows fair development, pallor, opisthotonos, no tâche, marked bulging of anterior fontanelle, irregularity of pupils, neck very rigid. Chest shows harsh breath sounds at both apices and moist rales all over lungs. Breathing of Cheyne-Stokes type. Heart action regular, abdomen negative. Kernig's sign positive.

After lumbar punctures there was less bulging of the fontanelle. Puncture yielded turbid fluid under increased pressure.

Dr. Wolferth reported numerous bacilli free in the fluid with practically no phagocytosis. These cultures were thoroughly studied and afterward reported as influenzal bacillus of the meningeal type in pure culture.

This patient lived for three days after admission to the hospital. He had frequent convulsions and attacks of vomiting and was stuporous throughout. The temperature varied from 102° to 105°, the pulse from 130 to 165, and the respiration from 36 to 45. The treatment included stimulation, hot packs and baths, and urotropin.

A summary of the literature on influenzal meningitis shows that this disease is not rare, that it has an extremely high mortality rate, that the majority of cases occur in infants or young children, and that the death rate is higher in the young; that it cannot be distinguished from other forms of meningitis except by bacteriological examination of the cerebrospinal fluid; that the bacilli pass freely from the cerebrospinal space to the general circulation and cause a general bacteremia, and that secondary infections in the various organs are common.

The following recoveries are reported:

1. Langer. *Jahrb. Kinderheilk.*, 1903–91. Age, nine years. Ill twenty-seven days. (Recommends lumbar puncture.)
2. Caccia. *Monat. f. Kinderheilk.*, 1903–41. (Mya.) *Gaz. degli Osped.*, 1903, XXVI, 269. Age, nine months. Ill forty-two days. (Believe recovery the result of repeated lumbar puncture.)
3. Thomesco and Grascaski. *Rev. Neurologique*, 1904. Age, seven years. Ill ten days.
4. Cohoe. AM. JOUR. MED. SC., 1901, cxxxvii, 74. Age, thirty-three years. Ill thirty-four days.
5. Batten. *Lancet*, 1910, 1677. Age, fourteen months. Ill seventeen days.
6. Hill and Packard. *Lancet-Clinic*, June 26, 1915. Age, four months. Ill thirteen days. (Note marked improvement in condition following lumbar punctures.)
7. Klinger. 1912. Age, twenty-six years. Injection of electrargol (intravenous), daily for one week.

A personal communication from Dr. Packard of Philadelphia tells me of a case in which there was an infection of the middle ear and mastoid of a child. Symptoms of spinal meningitis prompted lumbar puncture, and a turbid fluid, under high pressure, was obtained which yielded influenza bacilli in pure culture. The symptoms cleared up, and the fluid became clear after four injections of influenza serum furnished by the Rockefeller Institute. This patient later had a complication of a brain abscess, with infection of a different type, which also ended in recovery.

This case will later be reported in detail.

Regarding treatment, there are three measures recommended which deserve serious consideration.

1. The anti-influenzal serum of Wollstein, whose action appears to be specific. Where practical, this serum should certainly be tried.
2. Hexamethylenamin, which has been recommended by a number of writers, notably Brem and Zeiler, and by Batten. The latter reports a case in which recovery followed its use. There seems, however, to be less basis for regarding it of great value than is the case with either Wollstein's serum or repeated spinal puncture and drainage.
3. Repeated lumbar puncture.

Drainage of the subarachnoid space by means of lumbar puncture has been practised extensively since it was first proposed by Quincke. Many writers make the assertion that in meningitis this procedure may relieve pressure symptoms, but can have no curative effect. In view of the reports of severe cases of meningitis, even of the pneumococcic and tuberculous varieties, showing recovery following repeated lumbar puncture, these statements seem unwarranted. There is an immediate and very striking temporary good effect, probably due directly to the relief of excessive intracranial tension and improved blood supply in the tissues of the brain and cord. There is also removal of the toxins which would otherwise be absorbed into the circulation. Improvement in the circulatory conditions following decreased pressure may have an effect in combating local infection. It is believed that under normal conditions the cells of the choroid plexus, in secreting the cerebrospinal fluid, act as an effective barrier to most toxins and antibodies. It has not, as far as I know, been demonstrated that antibodies do not pass into the spinal fluid in cases of meningitis where there is an active inflammation of the membranes, and leukocytes pour into the fluid in enormous numbers, and the conditions are far from normal. The increased phagocytosis and decrease in organisms which has been demonstrated following lumbar puncture suggest that with the resulting lowered pressure, and increased outpouring of fluid into the cerebrospinal space, protective substances may pass from the circulation into the spinal fluid.

A further benefit probably derived from frequent spinal drainage is protection in part against the development of that much feared complication of meningitis—internal hydrocephalus—as the rapid flow of fluid from the ventricles tends to keep the foremen of Majendie clear of exudate which might cause obstruction at this point.

In my case there appeared to be temporary improvement following the use of antimeniningococcic serum, which was employed before the culture reports showed the nature of the infection. This, of course, may have been partially due to the removal of spinal fluid, or to the effect of the serum, or independent of either. Following the use of anti-influenzal serum, the improvement was very striking for two days. Simple lumbar puncture and drainage was substituted for the serum treatment on account of the severity of the pain following the introduction of the serum. Had improvement not been satisfactory under this procedure, serum would have again been used, possibly with a previous introduction of novocain.

The spinal fluid was withdrawn slowly until marked discomfort was caused by temporal headache. The pressure was measured by a glass tube of small caliber connected with the needle. It was noted that at each tapping the pressure could be reduced about one-half before uncomfortable symptoms developed.

A review of the cases which have recovered seems to emphasize the value of lumbar puncture as a therapeutic measure in meningitis, and experimental results indicate that the anti-influenzal serum there is available a specific agent which should be employed in meningitis due to the influenza bacillus.

TUBERCULOSIS OF THE TONGUE.

By James R. Scott, M.D., Ph.D.,
MICROSCOPIST, ARMY MEDICAL MUSEUM.

(From the Pathological Laboratory of the Army Medical Museum.)

While it has long been an accepted teaching that the predilection of tuberculosis for certain organs and tissues of the body is one of the most striking features of that disease, it has been equally appreciated that the frequency of infection of a particular tissue varies directly with the organ under consideration. Tuberculous disease of the tongue, like tuberculous infection of any muscular tissue, has been considered one of the rare manifestations of tuberculosis in the human body. Probably the first recognition of tuberculosis affecting the tongue was that of Morgagni in the year 1767.[1] Louis discusses tuberculosis of the tongue, writing in 1825.[2] The first published account of individual cases of the disease is ascribed by most medical writers to Sir James Paget in 1858.[3] However, some eight years previously, Dr. Christopher Fleming of Dublin, related three cases of what he termed "tubercular" or "lupoid disease" of the tongue, in a paper upon "Inflammatory and Other Affections of the Tongue."[4] The rarity of the disease is attested by the fact that Bryson-Delavar was able to report only 47 collected cases at the International Congress on Laryngology in Philadelphia in 1886. Wedenski[5] was able to collect only 112 cases in 1895. As a result of a careful search of the literature as indicated by the *Index Catalogue of the Surgeon General's Library*, I have been able to collect 231 cases up to the present time.

Concerning the rarity of the disease, all authors are agreed in their opinions as to the infrequency with which this condition is met. Latham,[6] in a paper read before the International Congress of Medicine held in Lisbon in 1905, states that laryngeal tuberculosis is found in about one-fourth of all cases of clearly defined pulmonary tuberculosis, and from this fact is inclined to reason that lingual tuberculosis is more frequent than one would judge from the literature. Other authorities consider it to be very rare, and this consideration seems to be justified by the results of large series of autopsy reports. For instance, Willegk found only 2 cases of lingual tuberculosis during 1317 autopsies performed upon tuberculous subjects, Fisher but 6 cases in 1500 autopsies, and

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[1] Morgagni, De sedibus et causis morborum per anatomem indigatis, 1767.

[2] Louis, Traité de la tubercolose, 1825.

[3] Paget, Med. Times and Gaz., 1858.

[4] Fleming, Dublin Quart. Jour., 1850, x, 87.

[5] Meditzinskoje Obozrenije, Warsaw, 1895, No. 3.

[6] Congres international de medicine, Lisbonne, 1906.

Chiari, who has met with the greatest frequency of the lesion, reports only 12 cases among 625 tubercular subjects. As regards the frequency of the disease in America, I have been able to obtain access to the reports of 27 cases of this condition, although there are two other articles upon this subject in American medical literature,[7] [8] to which I was unable to obtain access. Apparently the first case of this disease was recognized in America by Tolland, of San Francisco, in the year 1859.[9]

The case which I have to report is that of a soldier, a private in the signal corps, aged thirty-two years. The following history accompanied the specimen which was sent to us for histological examination. The family history shows that the father and mother are living and in good health, with one brother and one sister living, and apparently free from disease. One sister, aged twenty years, and one brother, aged thirty years, died from pulmonary tuberculosis. The patient suffered from diphtheria before his twelfth year. He had always been predisposed to bronchitis, but the attacks were never of long duration. He indulges moderately in alcoholic stimulants, usually beer, and smokes cigarettes. His medical history during his nine years of service in the army shows that he suffered a fracture of the hand in 1905, was treated for myopia in 1907, and was carried on the sick report for three days in April, 1909, for acute laryngitis. The present trouble dates back four years. He states that at this time he visited a dentist to have his teeth cleaned. He noticed a small elevated white area on the left border of the tongue. After about two weeks he went to the hospital for treatment. The surgeon advised touching with tincture of iodin twice a week. He continued this treatment for a few weeks. Since then his blood has been examined many times, but the Wassermann has always been negative. Since the process has been present, this man has been twice enlisted, the first time three years ago and the second but a few weeks ago. The ulceration of the tongue was noted at his enlistment three years ago.

The physical signs are as follows: postcervical adenopathy, more marked on the left side; slight epitrochlear and inguinal adenopathy; few moist rales at the midaxillary line in the fourth interspace; vocal fremitus slightly increased in the left supraclavicular region. Patient is well-nourished, muscular, and the movements of the chest are equal on both sides. Palpation shows no change in the vocal fremitus. Percussion is the same on both sides, except that the note on direct percussion of the right clavicle is slightly higher than on the left. Auscultation, vocal resonance slightly increased posteriorly, right side to third rib and above the clavicle. After expiration and coughing, fine moist rales are heard over the apex of the left lung to second rib. Temperature, pulse, and respiration normal. The tongue was slightly enlarged, elevated, corrugated, and ulcerated; the ulcer occupied the posterior two-thirds of the tongue; increased slowly in size; not painful. The sputum was found positive for tubercle bacilli March 7, 1915.

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[7] Harsha, Illinois Med. Jour., Springfield, 1908, xiv, 270.

[8] Trimble, Jour. Cutan Dis., xxxii, 199.

[9] Tolland, Pacific Med. and Surg. Jour., 1859, ii, 370.

A small portion of this ulcerated area was excised and sent to the pathological laboratory of the U. S. Army Medical School for microscopic study and diagnosis. The tissue was hardened in 10 per cent. formalin, embedded in paraffin, sections cut and stained by the ordinary histological methods; also a number of sections were stained by a modified Ziehl-Nielsen stain for the demonstration of tubercle bacilli.

Microscopic Report. The surface of the section is covered by normal stratified squamous epithelium, excepting at the area denuded by the ulceration, where the epithelium has completely disappeared. Just beneath this denuded area is to be found an accumulation of young fibroblastic cells surrounding a small area of necrosis. Here and there among the fibroblastic cells are found foreign-body giant cells. Surrounding these areas there is a varying degree of round-cell accumulation. Deeper down in the section there are to be seen numerous smaller or larger tubercles, separating and pushing apart the muscular elements of the tongue. Some of the tubercles are situated in the connective tissue which unites the muscle bundles, but in some areas the tubercle formation has encroached upon and invaded true muscle tissue. Upon examining the sections stained by the Ziehl-Nielsen method there are to be seen numerous acid-fast bacilli. Of these bacilli some are located within the cytoplasm of the giant cells while others are found sparsely scattered through the ground substance of the granulomatous area. Diagnosis, tuberculosis of the tongue.

The patient was then transferred to the Army General Hospital at Fort Bayard, New Mexico, with the diagnosis, chronic tuberculous infiltration of the apex of the left lung; tuberculous ulceration of the posterior two-thirds of the tongue. Here it was established that he suffered from tuberculous involvement of both lungs.

In the consideration of the history of this case the impressive factor is the existence of the lingual lesion for a period of over four years, during which time the man was examined for evidences of pulmonary tuberculosis, with negative results. The finding of tubercle bacilli in the sputum in March, 1915, is not necessarily an indication of pulmonary involvement, since the sputum might have become infected while passing over the ulcerated surface of the tongue. May we consider then, in view of the long duration of the lingual process and the recent development of pulmonary symptoms, that we are here concerned with a primary tuberculosis of the tongue, and that the lungs were involved secondarily?

Tuberculous lesions of the tongue were thought by the older medical authors to occur chiefly in patients of advanced age, especially from forty-five years onward. That the majority of the reported cases fall within the age periods from forty to eighty years is true, but it must not be supposed that the disease is entirely confined to this period, since it occurs in all periods of life, from the first to the last decades, as is seen from the literature. The earliest age noted is in the case reported by Sinibaldi,[10] occurring in a child aged five and a half years. Moreover, in studying a large series of cases one is impressed by the fact that a fairly large proportion of cases occur during the earlier years of life, *i. e.*, before the age of forty years.

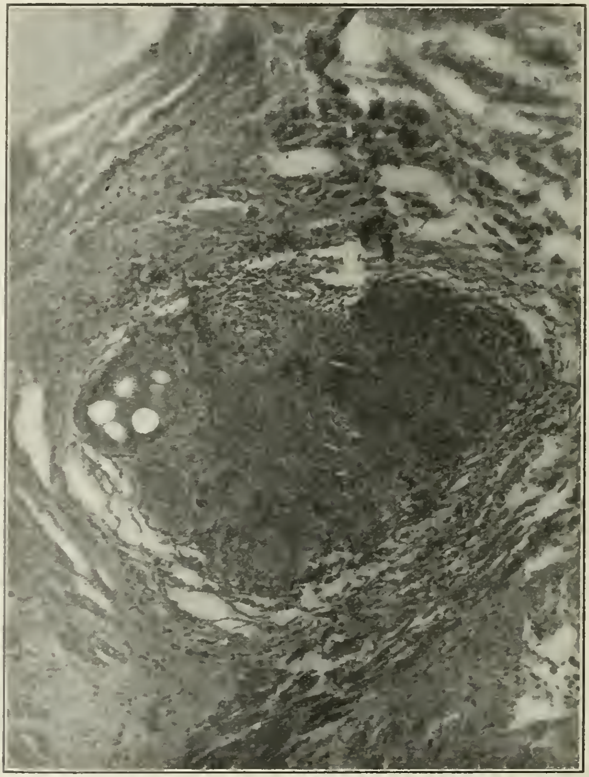

Fig. 1.—Photomicrograph showing a typical granulomatous area of the tongue. Giant cells at right, caseation in the centre, large giant cell containing vacuoles to the left. Magnification about 1000 diameters.

INCIDENCE OF TUBERCULOSIS BY AGE PERIODS.

1–9	10–19	20–29	30–39	40–49	50–59	60–69	70
1	5	11	12	27	18	6	–

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[10] Tommasi, 1908, iii, 232.

With regard to the relationship of the disease to sex it is not at all surprising to find that the majority of the reported cases have occurred in males while there is only an occasional case in the female. This is probably to be explained upon the assumption that in the etiology of this condition local trauma is an important predisposing factor. Males, due to the fact that they are often engaged in occupations which furnish an opportunity for the habitual carrying of miscellaneous articles in the mouth, such as nails by carpenters and shoemakers, very frequently suffer from small wounds of the mucosa of the tongue, thus setting up an area of impaired resistance in which subsequently the tuberculous infection may localize and develop. In the female also wounding of the tongue, as by pins, may act as a predisposing factor, but this is not nearly as frequent in the female as in the male sex. The sex incidence of the disease has been quoted by various authors as being four in the male to one in the female. In the series of cases collected, including only those cases in which the sex of the patient is stated, the ratio of males to females stands as 5.3 to 1.

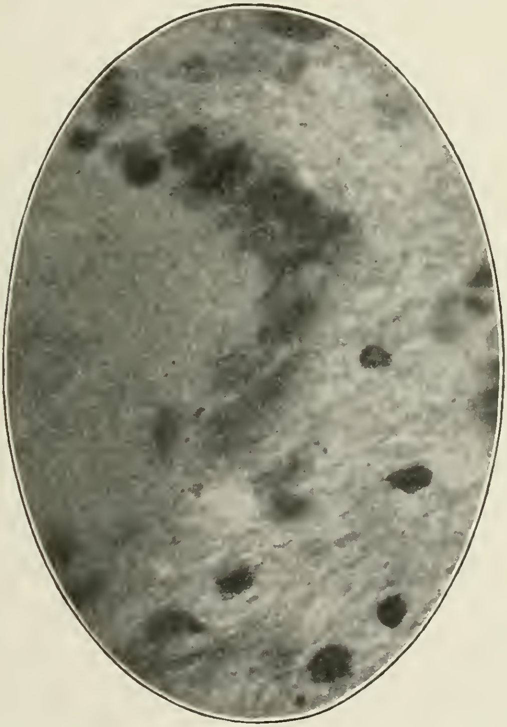

FIG. 2.—Photomicrograph showing giant cell, in which are found two tubercle bacilli. Magnification about 2000 diameters.

Concerning the etiology of the process, we must all agree that the essential factor in the condition is the deposition and proliferation of the tubercle bacillus in the tissues of the tongue. However, we must first accept that there are two main forms of the disease, the primary and the secondary, for the etiology must necessarily vary in respect to the two forms. In the secondary form, which is by far the most common form of the disease, the etiological factor of some moment is trauma. Trauma as mentioned above may cause a solution of continuity of the mucosa covering the tongue, and when this occurs in a patient suffering from pulmonary tuberculosis the lacerated tissues may be directly inoculated by the passage of bacilli-laden sputum over the inflamed area, with a deposition of some bacilli in the exposed area. This trauma may arise from various causes, the injury to the tongue produced by carrying of various metallic objects in the mouth, such as nails, or again from the constant irritation of a ragged and roughened carious tooth, which will in due time cause a chronic inflammation with the formation of a local area of ulceration. Carious teeth have been regarded as a possible etiological factor in 16 of the collected cases, while simple sudden trauma, as biting of the tongue, is mentioned in but seven cases. In a few of the cases reported, it has been noted that the patient has been a smoker, the majority of these being cigarette smokers. It is rather difficult to see just what role cigarette smoking could play in this lesion, since cigarette smoking is more prone to cause a generalized smoker's pharyngitis, while burning of the tongue is generally caused by a hot pipe stem. Moreover, as signifying the relative unimportance of smoking as an etiological factor, stress is placed upon smoking in only four of the cases collected. Once having produced an area of lowered resistance, the infection must be carried to this area in one of three ways: (1) there may have been direct inoculation of the surface by the passage of bacilli-laden sputum, as might occur in cases with coincident pulmonary tuberculosis, or of direct inoculation from food containing tubercle bacilli; (2) the infection may have been carried to the tongue through the blood stream, although the proof of this form of etiology is somewhat difficult; (3) the infection may have been carried by the lymph stream, which seems to be a possible explanation of a certain number of cases. Inhalation of the bacilli seems to be of little importance in the secondary form, and is probably a negligible factor. By far the greatest number of cases of secondary lingual tuberculosis is due to the inoculation of a wound in the tongue by bacilli from the sputum, but a small number of cases doubtless arises by the extension by direct continuity of a tuberculosis of the oral cavity, larynx, and pharynx.

The primary tuberculous ulcer is much more rare than the secondary form. In a series of 231 cases collected from the literature

I was able to find only 26 undoubted cases of the primary form. The difficulty of considering any given case as a primary one is increased by the fact that many times tuberculosis of the internal organs may give rise to no symptoms during the early stages, or that the symptoms are so indefinite that tuberculosis is overlooked. True primary tuberculosis of the tongue would necessarily be caused by the wounding of the tongue by some instrument contaminated by tubercle bacilli, by the infection of an existing ulcer with tubercle bacilli in the food or drink, or by the inhalation of the bacilli, with a deposition upon the tongue and a subsequent proliferation.

The symptoms of tuberculous ulcer of the tongue present much in common with other ulcerative processes in this locality. One of the most striking characteristics is the indolency of the condition, since the ulcerated area does not appear to enlarge with any rapidity, neither does it respond to local treatment. At the onset there is little enlargement of the tongue and very little pain. With the progress of the disease the tongue becomes considerably swollen and its surface becomes covered by a glairy, grayish mucus. Shortly the factor of pain appears. At first this is only evidenced upon the ingestion of solid food, but after a varying period of time the pain becomes so intense that mastication is impossible and a liquid diet must be provided. After a time this soft diet also causes pain and discomfort, and even simple phonation is attended by excruciating pain. Coincidentally with painful phonation, appears salivation.

The tuberculous lesion is generally localized in the neighborhood of the tip of the tongue, but may occur on the border of the organ or on either the superior or inferior surface at a varying distance back from the tip. The lesions are most frequently found upon the superior surface, but are occasionally seen upon the inferior surface. In most instances there is but one lesion at the onset of the process, but there may be two or more. As a rule, the lesion occurs as a small, rounded, slightly elevated nodule covered by normal mucosa. The form of the swelling is frequently irregular; when small in size it is either round or oval, but when large it may be rectangular or very irregular in outline. This nodule rapidly breaks down in the centre and forms an ulcerating area. The walls of the ulcer are generally abrupt and frequently are undermined. The surface of the ulcer is covered with a sticky mucus. Upon removal of this mucus there is revealed a gray or yellowish-red, at times a reddish, ulcerated surface, which presents small, hard, round prominences which suggest granulation tissue. Later, other similar ulcers may be formed in the vicinity of the first, and as these break down the single ulcers may coalesce to form a large irregular, serpiginous ulcerated area. Very frequently the process may extend and involve the neighboring lymphatic glands, although this is by no means an invariable rule.

The tuberculous process may occur in the form of a granuloma proper, but it is to be noted that this form of the infection is rare. The French authors report a few cases of this form under the caption "gommateuse" tuberculosis. It most frequently arises as a small nodule on the side or superior surface of the tongue, which gradually increases in size until in some cases it may occupy as much as one-half the extent of the tongue. The nodule is covered by normal-appearing lingual mucous membrane. Superficial ulceration does not appear as an early sign in this form of the disease. Microscopically this form presents the usual picture of a granuloma, a slightly necrotic centre, surrounded by an area of slightly proliferated endothelial cells, enmeshed in which are a varying number of young connective-tissue cells, the whole being surrounded by a zone of inflammatory round cells. In some cases a few typical giant cells may be discovered in the zone of endothelial leukocytes, and occasionally the tubercle bacilli may be demonstrated in these granulomatous areas.

In the fissured form the chief characteristic is the occurrence of fissures either at the tip or at the sides of the tongue. These vary in length, generally being short and frequently branched. There is generally found but one fissure, which may present several branches. Very rarely the fissures are multiple. The fissures appear as linear ulcers rather than as true fissures, since there is very little tendency toward the formation of vascular granulation tissue, as is characteristic of the true fissure. Upon separating the edges of the fissure it is found that the depth and breadth of the fissure is far greater than appeared from the superficial examination. The walls and sides of the fissures are prone to undergo necrosis, thus converting the walls into a ragged and irregular surface. In the tissue surrounding the fissure there may be found one or more small yellowish or grayish points or nodules, which sooner or later break down to form the typical tuberculous ulcer.

Another and very rarely observed form of the disease is the so-called papillomatous form. Of this there have been reported up to the present time only about 6 cases. In this form the first evidence of the disease is the appearance of a small papilloma, or in some cases the papillomata are multiple. The papillomata are, as a rule, indistinguishable from the ordinary papilloma, and indeed often lead the diagnostician to lean toward the idea of malignancy. These papillomata may retain their characteristics, in which case the diagnosis of tuberculosis is only arrived at during the microscopic examination of material from the lesion, or the papilloma may break down and ulcerate, eventually exhibiting the characters of the tubercular ulcer.

The signs of the disease include the evident lesion, which has been described in its varying forms. Aside from the local lesion the lymphatic glands beneath the jaw are enlarged in a certain percentage of cases, but by no means in all cases. Cachexia is occasionally seen in these cases, but cachexia is most often seen in cases where lingual tuberculosis is secondary to a pulmonary tuberculosis, and it is probable that the cachexia is dependent upon the primary disease. As is noticed in pulmonary tuberculosis, there is some night sweating, loss of weight, and a general feeling of fatigue, but it is very difficult to know how much these symptoms and signs are dependent upon the lingual lesion and how much upon the primary disease, since they appear to be most definitely shown in cases where the lingual process is secondary.

The differential diagnosis of tuberculous disease of the tongue from other affections is often a matter of considerable difficulty. In the series of cases collected the diagnosis was frequently made only after the microscopic examination of material from the lesion. The differential diagnosis involves consideration of the simple ulcers of the tongue, the local manifestations of syphilis, and carcinoma. The exclusion of the simple ulcers, as the aphthous, is a matter of slight difficulty, as tuberculous ulcers are notorious for the fact that local palliative measures are without effect, whereas such simple measures usually suffice for the cure of simple ulcers. The syphilitic ulcer must be excluded by the fact of a negative Wassermann reaction, by the lack of response to potassium iodide and other antiluetic measures, and by the absence of other signs and symptoms of lues. It must, however, always be borne in mind that there may be a tuberculous ulceration of the tongue in a patient who is a victim of lues. In such cases the diagnosis of the tuberculous nature of the lesion would be made on the lack of response of the local ulcer to the antiluetic treatment. In carcinoma of the tongue we meet with great difficulty in establishing the diagnosis. The diagnosis between these two conditions must be finally made by the microscopic examination of the tissue itself whereby the cellular picture would definitely exclude the consideration of carcinoma. However, the microscopic differentiation between gumma and tuberculoma is very difficult if not impossible. In this case, sections of the tissue should be subjected to the special staining methods to demonstrate tubercle bacilli, and in cases where the material has reached the laboratory in a fresh or unfixed condition it should be a matter of routine practice to grind up a bit of the tissue in a sterile mortar, emulsify with physiological saline, and inject a suitable quantity into a guinea-pig, the biological test. Very frequently guinea-pigs treated in this way will die from a generalized tuberculosis when one has been unable to demonstrate the bacilli in the sections of the lesion. In the series of 231 cases collected the tubercle bacilli were demonstrated in the tissues in only 42 cases. Even after having taken all these precautions, it may at times be impossible to say that a given case is tuberculous. In diagnosing the tuberculous lesion of the tongue as primary, one proceeds merely by the fact that no other focus of tuberculosis can be demonstrated to exist in the body.

The prognosis depends, of course, upon many factors aside from the simple ulceration of the tongue. The home life and the hygienic conditions of the patient are important. The lesion itself has for a long time been considered serious, and the older physicians were unanimous in according it a bad prognosis. However, if taken in its earlier stages, and if the patient be not suffering from pulmonary tuberculosis in an advanced stage, surgical removal of the diseased portion of the tongue often results in an apparent cure. In cases of the disease with concomitant involvement of the lungs or other parts of the respiratory system the treatment must be hygienic and supportive, and the prognosis under these conditions is almost hopeless. Von Ruck, however, believes that even in fairly advanced cases, the prognosis is fair when tuberculin is administered.[11]

When we come to consider the manner of treatment for lingual tuberculosis we find ourselves face to face with a problem of great difficulty. If we make an attempt to study the literature to discover the most satisfactory form of treatment we find nearly as many views as there are authors in this particular field of medical literature. Like pulmonary tuberculosis it has been treated with every conceivable therapeutic measure and by a variety of surgical procedures.

Considering the medical treatment of the lesion, we first learn that during the early days of the recognition of lingual tuberculosis as a separate entity the medical profession placed its faith in simple medical means, such as caustics of various nature. Of these, silver nitrate was one of the first to be used. The use of silver nitrate is often attended by a temporary improvement of the condition, in some cases leading to an apparently complete healing, but is invariably followed by a recrudescence of the condition, with greater ulceration, and on the whole is very unsatisfactory. Lactic acid, phenol and alcohol, and tincture of iodin have been used, and while a number of French physicians report good results from these measures, the majority of those who have employed these remedies report unfavorable results. Potassium iodide has been much used, but without permanent effects upon the condition. Von Ruck reports very good results in this condition by the use of tuberculin in suitably graded doses. He reports having effected a cure in 4 cases of lingual tuberculosis by means of tuberculin.[12] Lagomarasino[13] has reported the cure of a case of primary tuberculosis of the tongue by the administration of the vaccine of Denys-Delys. A few authors report having tested the efficacy of the Roentgen and ultraviolet rays in this condition, but again the majority of such treatments have furnished no grounds for hope of ultimate success along these lines. Very recently, however, Stropeni has reported a primary case of tuberculosis of the tongue which was entirely cured by the application of the Roentgen ray.[14] Radium has been tried to a slight extent, but at the present time, while perhaps a little early to form a final opinion, the hopes of success are not particularly bright.

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[11] Von Ruck, Laryngoscope, 1912, xxii, 1190.

[12] Loc. cit.

[13] Semana Méd., 1912, xix, 1216.

The surgical treatment is advocated at the present time by the majority of medical men who have treated this lesion, although there is some diversity of opinion as to the exact measures to be chosen. Among the first who operated for this condition it was held necessary to perform a ligation of the lingual artery at some time before the main excision of the tongue was made. As surgical knowledge increased and technic improved the ligation was omitted and the tongue amputated in the usual manner. In cases in which the lesion occupies only the anterior portion of the tongue it is now the practice to remove a V-shaped piece of lingual tissue, going far beyond the limits of the actual lesion. In cases in which the greater part of the tissue of the tongue is affected it is, of course, necessary to completely amputate the tongue, and the chances of ultimate success are much decreased. Simple curetment of the ulcer is not advisable, as the curet merely opens the lymphatic vessels and channels of the tongue, with the inevitable result that the bacilli are crushed into such channels, resulting either in a recurrence of the disease or in a more serious generalization of the tubercular process. The Pacquelin cautery has been used in some cases, and is a much better method of local conservative treatment than curetment.

Conclusions. 1. Tuberculosis of the tongue is of more common occurrence than is commonly supposed, and occurs more frequently in males than in females, probably from the fact that males are more prone to carry miscellaneous objects in the mouth.

2. While the disease occurs during all age periods of life, it is most common during the decade from forty to fifty years.

3. It occurs in two forms, primary and secondary. The greater number of cases are secondary in character. Clinically it may assume different types, as the ulcerated, fissured, the granulomatous, and the papillomatous.

4. The differential diagnosis involves consideration of simple ulcers, the local manifestations of lues, carcinoma, and epithelioma.

5. The treatment may be either medical or surgical. Medical treatment offers little hope of ultimate cure, and should only be used in advanced cases, or when the lingual process is accompanied by a generalized tuberculosis. The rational treatment is surgical in nature, with complete excision of the involved tissues and the surrounding healthy tissues for some distance.

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[14] Stropeni, Policlinico, Roma, 1915, xxii, 157.

ADDISON'S DISEASE: REPORT OF A CASE WITH ACUTE ONSET, TERMINATING IN RAPID IMPROVEMENT AND COMPLETE RECOVERY.

By Theodore Tieken, M.D.,
PROFESSOR OF THERAPEUTICS, RUSH MEDICAL COLLEGE.

I wish to report a case of Addison's disease, in a young man, which ran an acute febrile course, with nausea, vomiting, diarrhea, and marked asthenia. There was pigmentation of the skin, a low blood-pressure, loss in weight, pain in the abdomen and lumbar regions, anemia, insomnia, and marked cerebral disturbance. After a period of six weeks the patient began to improve, and made a rapid recovery.

History. J. L. K., male, aged thirty-six years, a butcher by occupation, presented himself at the Cook County Hospital, August 10, 1912, on account of a urethral stricture, cystitis, and an ascending pyelitis involving the left kidney.

Cystoscopic examination at this time showed a stricture of the anterior urethra (which was readily dilated), a severe cystitis, inflammation about the left ureteral opening, from which flowed cloudy urine containing pus and blood. A catheterized specimen showed many streptococci and colon bacilli, but a most searching examination failed to reveal any tubercle bacilli. Urine from the right kidney was normal.

Under the usual antiseptic treatment, with bladder irrigation and rest in bed, the patient made a rapid recovery, leaving the hospital in thirty days. He remained well for nearly a year.

On August 12, 1913, a year later, he suddenly experienced a severe pain in the left lumbar region. At first this was of a dull, aching character; later, sharp and lancinating, radiating downward to the bladder and genitals. It became so severe that he went to bed and called a physician, who treated him for six days without relief. On the sixth day the patient had a chill lasting half an hour, followed by high fever, nausea, vomiting, and severe pain in the right lumbar region. Urination became more frequent and difficult, there was pain at the neck of the bladder, and a constant desire to urinate. Although urination was frequent, only a little foul-smelling, stringy urine was passed, and this, at times, contained blood. Repeated chills followed and the patient rapidly grew worse. He was unable to sleep on account of pain, and asthenia developed rapidly.

On August 17, 1913, his friends told him his skin was turning brown. This frightened him, and he asked to be sent to the hospital.

Previous Illness. Patient has had the usual diseases of childhood and occasional pains in the back and shoulder which he calls "rheumatic." He has had no other serious illness except gonorrhea.

His first infection was mild and occurred eighteen years ago. A second infection occurred fifteen years ago. This was very severe and was followed by a urethral stricture, which has troubled him more or less for twelve years. Three years ago he suffered from retention of urine, necessitating the use of a metal catheter. Following this he had bladder trouble, from which he recovered after treatment. One year ago the patient had a recurrence of bladder trouble and was treated at the Cook County Hospital, as stated above.

He had a chancre fifteen years ago, followed by severe secondary symptoms, for which he took treatment and recovered.

Family History. Negative for tuberculosis, malignancy, and nervous trouble. There is no history of similar trouble in the family. Brothers and sisters are well. No history of alcoholism in the family, and the patient has always been very moderate in its use. Uses tobacco moderately, but is not addicted to the use of drugs.

Examination. Head shows no deformities or scars; hair is thin and glossy, and has been coming out freely since this illness began. Eyes are normal in appearance; the pupils equal, regular in outline, and react sluggishly to light and accommodation. There is no nystagmus or paralysis of the external muscles. The ears and nose are negative. The teeth are good; gums are slightly inflamed, but pyorrhea alveolaris is not present. Tongue is flabby, moist, and coated with a brownish fur, but no pigmentation is seen. The tonsils, larynx, pharynx, and buccal mucosa are negative. At the left angle of the mouth a few pigmented striæ are seen extending inward, otherwise the mucous membranes show no pigmentation.

The lymphatic glandular system is negative in the cervical, axillary, and inguinal regions.

Chest is symmetrical, long, and narrow. Expansion is good above but limited below on account of pain. Litten's phenomenon is absent on both sides. Respiration is shallow.

Palpation shows limitation motion on both sides, especially in the lower part. No friction rub felt and vocal fremitus is normal.

Percussion shows slight dulness over both apices and over the lower part of the left lower lobe, extending upward as far as the ninth rib posteriorly. The right side is normal posteriorly.

Auscultation shows a few small moist rales over both apices and in the left axillary region. Over the dull area on the left side there is no evidence of consolidation or fluid. Voice and breath sounds are transmitted normally and no friction rub is heard.

The area of cardiac dulness is normal; apex beat is in the normal position. Heart sounds are pure but rather distant and weak. No murmurs or friction rub heard, and the cardiac movement is not hindered by adhesions.

Pulse is rapid, weak, and easily compressible, but no irregularities are noted.

Blood-pressure on admission was extremely low. Systolic, 78. Diastolic could not be taken at this time, although both the Faught and Tycos instruments were used.

The abdomen is distended in the upper part, which shows pain, tenderness, and rigidity on palpation. Bimanual palpation reveals a distinct mass on both sides; deep pressure causes sharp pain, both anteriorly and posteriorly. The mass is firm, immovable, and feels more like an inflammatory exudate than a tumor. No edema of the subcutaneous structures is present.

The stomach is not enlarged; liver is palpable but not tender except over the gall-bladder, where pain is complained of on deep pressure. Spleen is negative.

The glans shows an old scar, otherwise the genitals are negative. No hernia is present.

Reflexes are all present and normal except the knee-jerk, which is somewhat exaggerated.

No sensory disturbances can be demonstrated.

Muscles are soft, flabby, and somewhat atrophied.

Skin is soft, moist, and free from eruptions or scars.

Pigmentation is general, but more marked on the exposed surfaces, as the hands and face. In the axillæ, at the waist line and in the pubic region, bronzing is more marked than on the trunk and extremities, while the genitals are almost black. Over the abdomen the skin shows the characteristic striations or "ribbing," like the sand on the seashore.

Pulse, temperature, and respiration were as follows:

August 17, 1913. Pulse, 120; temperature, 102.6; respiration, 28.
August 18, 1913. Pulse, 120; temperature, 104.6; respiration, 26.
August 19, 1913. Pulse, 105; temperature, 103.0; respiration, 22.
August 20, 1913. Pulse, 110; temperature, 102.4; respiration, 22.
August 24, 1913. Pulse, 112; temperature, 102.6; respiration, 22.

The pulse and temperature remained high for nearly three weeks; then both gradually receded, reaching normal on the twenty-eighth day in the hospital.

Blood-pressure remained below normal until the patient began to improve.

August 17, 1913. Systolic, 78; diastolic, 0.
August 18, 1913. Systolic, 78; diastolic, 60.
August 26, 1913. Systolic, 84; diastolic, 72.
August 30, 1913. Systolic, 94; diastolic, 70.
September 5, 1913. Systolic, 95; diastolic, 70.
September 27, 1913. Systolic, 124; diastolic, 80.
October 12, 1913. Systolic, 128; diastolic, 80.

Urine. Single specimen examined August 18, 1913, is cloudy, light in color, alkaline, strongly ammoniacal. Specific gravity, 1023. It contains albumin and blood, but no sugar, bile, or indican; urea is 1.2 per cent. Microscopical examination shows numerous pus cells, red blood corpuscles, degenerated epithelium, and many motile organisms. No casts were seen. A stained specimen of the sediment showed many streptococci and colon bacilli, but no tubercle bacilli. Later examinations made, using the antiformin method, were negative also.

Blood examinations showed the following:

August 18, 1913. Red cells, 2,240,000; leukocytes, 23,000; hemoglobin, 35 per cent.

August 26, 1913. Red cells, 2,220,000; leukocytes, 16,000; hemoglobin, 32 per cent.

September 21, 1913. Red cells, 3,330,000; leukocytes, 11,500; hemoglobin, 55 per cent.

October 10, 1913. Red cells, 3,600,000; leukocytes, 10,000; hemoglobin, 65 per cent.

Differential count of 200 cells shows: small mononuclears, 12 per cent.; large mononuclears, 6 per cent.; no eosinophiles; transitionals, 2 per cent.; polymorphonuclears, 80 per cent. Other examinations were made, but no eosinophilia was found.

Red cells showed nothing abnormal; no parasites were found; no basophilic degeneration present. Chemical tests for hypoglycemia were not made, although Porges has suggested that this should be done in all cases of Addison's disease, as he found such a condition in dogs after the adrenals had been removed.

Sputum was examined frequently for tubercle bacilli, but none was found. Tuberculin reaction was negative.

Stomach contents, after Ewald's test meal, withdrawn after one hour, showed, 40 c.c. in amount, well mixed, no mucus or blood.

Free hydrochloric, 1 c.c. decinormal sodium hydrate.

Combined, 10 c.c. decinormal sodium hydrate.

Total acidity, 11 c.c. decinormal sodium hydrate.

No lactic, acetic, or butyric acid found; no blood to the Weber test; no Oppler-Boas bacilli present.

Feces were liquid, contained no blood or intestinal parasites. At times much undigested food was present, but no mucus.

Course of Disease. Patient grew rapidly worse during the first week; fever was continuous and he had several chills, some lasting half an hour. Following each chill there was a rise in the temperature of 1° to 2° F., and a corresponding acceleration of the pulse. Patient complained of severe headache and weakness.

During the second week his condition became so alarming that we had little hope for recovery. The pulse became weaker, asthenia more marked, and a severe diarrhea with involuntaries came on.

Pigmentation was very pronounced now and the patient was indifferent to his surroundings. This condition continued until the end of the third week, when gradual improvement was noticed. He began to take an interest in his surroundings and expressed a desire for food. On the twenty-eighth day the morning temperature was normal, and on the thirty-first it remained so all day. After this improvement was rapid, and on the thirty-sixth day he was able to sit up a short time. In another week he was able to walk about the ward and remain up all day. During his convalescence he gained rapidly in weight and strength. The pigmentation gradually disappeared; first from the trunk and extremities; then from the face, hands, axillary, and girdle regions, where pigmentation is normally increased. The genitals were still darkly pigmented when he left the hospital, October 20, 1913.

On the day of his departure a blood examination showed 3,800,000 red cells; 12,000 leukocytes, and 68 per cent. hemoglobin. Blood-pressure was 128 systolic, 98 diastolic; pulse, 88; temperature, 98.6; respiration, 16.

I have kept in communication with him for two years, and he says his health was never better. He has worked regularly, eats and sleeps well, is free from pain, and weighs 156 pounds.

Pathogenesis. In this case I believe we are justified in assuming that the function of the adrenal glands was interfered with by an inflammatory exudate, caused by extension of the infection from the pelvis of both kidneys into the surrounding tissues, involving especially the medullary portion of the adrenals and the closely-associated, sympathetic ganglia. We know that the medulla of this gland supplies an internal secretion, epinephrin, which regulates blood-pressure and vascular tonus, and if kept out of the general circulation from any cause, symptoms of Addison's disease develop. The medulla is a part of the chromaffin system, is closely associated with certain metabolic processes, and is necessary to sustain life. Animals from which the adrenals have been removed die in a very short time (in two to four days).

Pigmentation of the skin began to develop on the sixth day and became more marked during the first month of the disease. As improvement occurred, it gradually grew less, and when the adrenals were able to functionate properly it disappeared.

It is generally believed that these glands are closely associated with pigmentation, but the chemistry of the process is not yet understood.

Goldzieher has shown that the adrenal function is disturbed much earlier in the presence of general sepsis. Our patient was certainly septic, as shown by repeated chills, high temperature, leukocytosis, with polymorphonuclear increase, and urinary findings.

Straub reports a case of Addison's disease in a patient suffering from carcinoma of the stomach and peritoneum, in whom thrombosis of the adrenal veins caused pigmentation to develop in seventeen days. Autopsy showed the thrombotic process to be of recent occurrence, and no doubt was the real cause of the sudden onset.

Chvostek reports a case in a young man, following a bilateral perinephric infection, which resulted in a total destruction of the adrenal glands, causing death in a very short time.

Sargent and Bernard report a case in a young man, with sudden onset, with sharp abdominal pains, nausea, vomiting, early collapse, marked psychical disturbances, and hypothermia. Death occurred in ten days.

Langmead reports a case of Addison's disease in a boy, ten years old, having all the clinical symptoms. Pigmentation had been noticed for about a year. During this time he had several attacks of diarrhea, marked asthenia, and hypothermia. The acute attack came on suddenly, with vomiting, restlessness, convulsions, rigidity, and all the symptoms of meningitis. The patient lived only a few hours after reaching the hospital. Autopsy showed bilateral caseous tuberculosis of the adrenals; a very small heart, weighing only three ounces; status lymphaticus, with enlargement of the thymus and hypertrophy of all the lymphatics.

Lowy reports a case, occurring in a young man twenty years old, which ran a very acute course. Autopsy showed apparently normal adrenals, but microscopic examination revealed a total absence of the specific cellular elements of the cortex of both glands. He believes that the cortex has an important function, and when diseased, Addison's disease results. .

Very recently I saw a young man with all the characteristic symptoms of Addison's disease except asthenia. He had worked at hard labor until two weeks before the onset, which was sudden, with severe pain in the abdomen, nausea, vomiting, diarrhea, marked restlessness, pigmentation of the skin and mucous membranes, low blood-pressure, and hypothermia. His muscular development and strength were extremely good until a few days before death, which occurred twenty days from onset of acute symptoms. Autopsy showed bilateral caseous tuberculosis of both kidneys and adrenals. No other foci of infection could be found.

"Our knowledge of these glands is chiefly confined to certain activities of the medullary proportion; of the cortex, we know practically nothing." (See recent article by J. Aikman.)

From an extensive description of the adrenal glands, their anatomy, histology. embryology, physiology, pathology, etc., published by one of the highest authorities on the subject, the late Dr. Edmund Neusser, professor of internal medicine at the University of Vienna, it is learned that these bodies were discovered by Eustachius in 1564, but that the first satisfactory theory as to their function was given by Addison in 1855.

"He first called attention to the relation existing between disease of these organs and a peculiar group of symptoms (Addison's disease), and expressed the opinion that their extensive destruction led to severe general disease and death."

Brown-Séquard, in 1856, experimented on animals, removing the adrenal glands and studying the symptoms following their extirpation in order to gain definite information regarding their function and thus to decide whether or not these organs were essential to life. After a series of investigations he concluded that they are absolutely necessary to life.

Later investigators contradicted his views, but from 1889 up to 1913 a number of other scientists supported the conclusions of Brown-Séquard, showing by various experiments that death resulted from removal of the adrenals, one observer having found extensive alterations in the brain, cerebellum, spinal cord, and peripheral nerves of animals thus experimented with, while another investigator decided that the organs in question possessed an extra-uterine function essential to life.

Neusser says: "It is evident that Brown-Séquard's view—that these organs are essential to life—is strongly upheld by the most recent experiments."

Regarding the function or physiology of the adrenals, physiologists have proposed three different ways in which to decide this question. The first method comprised the "clinical" observation of animals deprived of one of these organs, and included investigations concerning (1) nutrition; (2) temperature; (3) disturbances of the nervous system; (4) disturbances of the digestive organs; (5) changes in the blood; (6) the pulse respiration and blood-pressure; (7) changes in the skin and mucous membranes.

Neusser sums up the results of these observations, stating that as to nutrition, more or less emaciation in animals was noticed by a number of investigators. Concerning temperature, the conclusions are very diverse, some observers noting a fall of temperature, and, again, no great variation being detected.

As to the third condition, profound cerebral symptoms have been reported by various authorities, such as convulsions, delirium, vertigo; diminished motor power and reflexes; contractures of the anterior extremities; paralytic symptoms; loss of faradic nervous irritability (the direct muscular irritability being unimpaired), with death from paralysis of the muscles of respiration. One scientist failed to note convulsions after removal of the adrenals, observing, instead, apathy, rigidity, and weakness of the extremities, combined with difficult breathing.

Disturbances in the digestive organs included loss of appetite, increased peristalsis, and diarrhea.

Views differ regarding the changes in blood under the conditions in question, although the opinions as to the chemical alterations more nearly agree than those concerning the number of red and white corpuscles and the percentage of hemoglobin. According to the views of certain authorities the suprarenal capsules are neutralizing organs; their function being to destroy certain toxic substances which accumulate in the blood as the result of nervous and muscular activity; while another observer concluded that the adrenals are rather regulators of cell nutrition.

Concerning the pulse, respiration, and blood-pressure after extirpation of the adrenal glands it was found that while the pulse and respiration may not be constantly affected a fall of blood-pressure is observed.

A few investigators have noted certain changes in the skin and mucous membranes following extirpation of the adrenals, such as abnormal pigmentation.

The study of the action of suprarenal extracts formed the second method of deciding the function of the adrenals, and the principal effects by Oliver and Schaefer, who injected an aqueous extract and a glycerin extract into different animals, are stated by Neusser as follows:

"1. An enormous rise of blood-pressure, the result of excessive contraction of the bloodvessels. Stimulation of the depressor nerve during the administration of suprarenal extract failed to produce a fall of blood-pressure. It follows that the rise of blood-pressure is the result of a direct action of the extract upon the muscular fibers of the heart and arteries.

"2. Slowing and strengthening of the heart's action and pulse. These result from stimulation of the vagus centres. It is apparent that suprarenal extract increases the frequency of the heart's action.

"3. In frogs and mammals the duration of muscular contraction was lengthened. Its action upon respiration was inconstant. Extracts of the medullary portion of the capsules alone were active. Suprarenal extract from healthy human beings was very powerful, while the extract from two cases of Addison's disease was totally inert. These authors conclude that the suprarenal bodies elaborate an internal secretion which maintains the physiological tone of all the muscular tissues, especially of the heart and vessels."

Neusser also refers to the experiments of Szymonowicz and Cybulski with suprarenal extracts, and gives their conclusions as follows:

"1. Extirpation of both suprarenal capsules causes a decided fall of blood-pressure; the pulse becomes small.

"2. Intravenous injection of suprarenal extract causes a marked rise of blood-pressure with slowing and strengthening of the heart's action.

"3. The same symptoms, although less intense, are produced by the injection into the circulation of the blood of the suprarenal vein.

"4. The suprarenal body is an organ essential to life.

"5. The function of the suprarenal capsules is to elaborate and add to the blood a substance which stimulates the activity of the vasomotor centers, the centers of the vagus and accelerator nerves, and the respiratory centers, and permanently preserves the tonic tension of these centers.

"6. The theory of the neutralizing action of the suprarenal capsules can be dispensed with, for the loss of the above-mentioned tonic influence is sufficient to explain all symptoms occurring after their removal.

"The third method of physiological investigation is the chemical. For a technical description of this subject see Neusser's article as noted in the bibliography and the bibliographical references on 'epinephrin,' 'suprarenin,' and 'adrenalin.' "

As the cause of Addison's disease, Dr. F. Pfletschinger, in a recent article, refers to the theory advanced by Neusser that the adrenals, the spinal cord, and sympathetic system are all interrelated, and that injury of any of the three would break the connection and produce Addison's disease, and then adds:

"Wiesel, in 1903, made the next big advance—he drew attention not so much to the sympathetic but to the intercorrelated adrenal system and accessory adrenal glands. They are composed of osmium staining lipoid cells, similar to those of the cortex in adrenals and similar to nerve cells in general. These accessory glands contain no medullary cells like those in the medulla of adrenals. But there are many medullary cells found in the ganglia of the abdominal sympathetic and intercarotid ganglia, along the entire sympathetic system in fact, partly as individual cells and partly as small masses, viz., Zuckerkandl's gland at the bifurcation of the abdominal aorta. On account of their staining qualities these are known as chromaffin cells, and together with the medulla of adrenal are known as the chromaffin system.

"Wiesel cites six cases of Addison's disease which he investigated minutely, and in which he found destruction of chromaffin cells in the medulla of the adrenals and in the sympathetic. The cortex of the adrenals and the accessory adrenals was found intact or slightly affected. He cites also one case of tuberculosis of both adrenals without symptoms of Addison's disease, in which he found hypertrophy of chromaffin cells in the sympathetic. He therefore considers Addison's disease a specific disease of the chromaffin system."

Pfletschinger further says that other observers consider the cortex of first importance, and that cases have been cited in which, with tuberculosis of both adrenals without symptoms, hypertrophy of the cortical substance was found. Still another writer, he says, maintains that disturbance of the function of the adrenals is the only cause of Addison's disease which may arise from disease of the glands or of secretory nerves. Also, Neusser and Wiesel draw attention to the frequency of the combination of Addison's disease and the lymphatic diathesis with hypoplastic constitution, and declare that the primary underdevelopment of the chromaffin system which is present in hypoplastic constitutions is conducive to the development of Addison's disease.

"As far as animal experimentation goes, some experiments show medulla necessary to life, some show cortex. The cause of death after complete removal is unknown, but is very prompt in two to four days."

Pfletschinger, in concluding his remarks on the cause of the disease in question, says:

"The most plausible theory today is Wiesel's, that Addison's disease is due to destruction of the chromaffin system."

For an exhaustive discussion of the various theories as to the cause of Addison's disease, see an article by Rolleston.[1]

H. A. Hare[2] says of the etiology of Addison's disease:

"The cause of Addison's disease is not known in the sense that we recognize a cause which is responsible for all cases. In about 50 per cent. of the cases so far reported which have come to autopsy, tuberculosis of the suprarenal glands has been found. That this lesion is not sufficient in all cases to cause the general systemic manifestations of the disease is proved by the fact that identical changes have been found in the suprarenal bodies when none of these symptoms have been present. In certain cases, hemorrhages into the suprarenal bodies as the result of injuries have caused the symptoms to develop.

"As a matter of fact, the view as to the relationship of these causes to the disease, expressed by Addison fifty years ago is probably correct—namely, that any lesion of these bodies which interferes with their function may cause the malady.

"In some instances the disease seems to be primarily the result of pathological changes in the semilunar ganglia of the abdominal sympathetic nervous system. Rolleston has expressed the plausible view that in these cases the disease arises in all probability by reason of the fact that the glands are cut off in circulation and nerve supply by growths or inflammatory exudates."

After further discussion of the subject of etiology, Hare says that the opinion generally held today is that the symptoms of Addison's disease manifest themselves because the suprarenal secretion fails to find its way into the general economy, and that changes in the sympathetic nervous system may also be a factor, and he adds the following statement:

"Finally, it is not to be forgotten that Addison's disease may be without noticeable lesions in the suprarenal bodies, and it is also a fact that these bodies may be almost completely destroyed by growth or by tuberculosis without any symptom of this malady developing."

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[1] Allbutt's System of Medicine.

[2] Practice of Medicine.

Rolleston sums up the situation as follows:

"Addison's disease is due to inadequacy of the chromaffin or adrenalin-secreting cells, which are chiefly situated in the medulla of the gland, but are also found in connection with the sympathetic trunks. It is possible that there is a second factor at work—namely, irritation of the sympathetic nerves—which might be (1) mechanical and due to adhesions and invasion of the pericapsular nerves and ganglia, or (2) toxic and due either to failure of a hypothetical antitoxic function of the cortex of the adrenals, or to disturbed metabolism resulting from absence of adrenalin."

DIAGNOSIS. A well-advanced case of Addison's disease should be recognized without difficulty, as there is no other condition which presents this typical symptom complex. However, early in the disease, before pigmentation has developed, many difficulties may be encountered.

Asthenia, anemia, loss of appetite, constipation, and a moderate degree of pigmentation may occur in pernicious anemia, and if the blood findings are atypical, one cannot make a positive diagnosis. The relatively high color index, more marked poikilocytosis and polychromatophilia, basophilic degeneration of the red cells and diminished coagulability, would speak more for pernicious anemia.

Tuberculosis of the intestinal tract with peritoneal involvement is frequently associated with pigmentation and must be excluded. This is sometimes difficult, as the tuberculous process may invade the adrenals and sympathetic system, thereby causing the Addisonian symptom complex to appear, making a differential diagnosis impossible.

Malarial cachexia with pigmentation of the skin must be excluded. Enlargement of the spleen, history of paroxysmal attacks, with chills, fever, and sweats, coming from an infected district and the finding of parasites in the blood, would make the diagnosis positive.

Vagabond's disease, miner's pigmentation, and other occupational diseases associated with the use of chemicals should readily be excluded.

Pellagra has been confused with it in some instances, but this should be excluded by the history, the spring and autumn exacerbations, increased appetite, the presence of other cases in institutions, and the characteristic dermatosis.

Bronzed diabetes, cirrhosis of the liver with pigmentation, Basedow's disease, chronic eczema, arsenical therapy, cancerous cachexia, and the pigmentation following Roentgen-ray exposures should be excluded without difficulty. We must remember also that pigmentation is normally increased in certain races.

THERAPY. We have no specific therapy today. Adrenal therapy has been disappointing, as shown by Adams, who collected 97 cases with the following results: Adrenal treatment with gland feeding, extracts, both glycerin and aqueous, by mouth and subcutaneously, caused some improvement in 31 cases; no improvement in 43 cases; made worse, 7 cases; permanent improvement was shown in 16 cases. In these the asthenia and gastro-intestinal disturbances were benefited, but no change occurred in the pigmentation.

In the case under consideration the treatment was purely symptomatic. The patient was made as comfortable as possible in bed and sponging ordered as needed for temperature. He was given a milk and egg diet with plenty of water. Hot compresses, frequently changed, were applied for pain in the back and abdomen.

For the bladder disturbance and pyelitis he was given 10 grains of hexamethylenamin, and 20 grains of sodium citrate, three times daily in water. Irrigation of the bladder was not necessary, as he responded quickly to internal medication.

For the bowels, ½ ounce of sodium phosphate crystals was given in hot water as needed. Tincture of hyoscyamus was given early for painful urination, in 15 minim doses three times daily; codein sulphate at night for pain and sleeplessness.

Very recently injections of pituitary extract have been given, with a hope that the pressor substance might act beneficially, but nothing has developed to justify any conclusion as to its merit.

A word of caution should be given in regard to the use of drastic purgatives for the obstinate constipation which sometimes occurs, as instances are recorded of sudden death from syncope and shock following such a procedure.

Greenhow reports a case in which Addison's disease was not suspected and sudden death resulted from the administration of a violent purgative.

For the diarrhea, vomiting, and syncope we should use the usual remedies for these conditions.

PROGNOSIS. All authorities consulted give a very unfavorable prognosis in Addison's disease, and especially so in the acute cases.

Dock[3] says: "Addison's disease is universally classed as a fatal affection; in fact, recoveries of genuine cases are so rare as to leave no other prognosis possible."

Eichhorst, in the last edition of his book, says: "Termination of this disease is so universally fatal that one needs scarcely speak of recovery."

Ebstein and Schwalbe say practically the same, and add that recoveries may be taken as mistaken diagnosis.

I realize that remissions occur in this as in other chronic diseases, but when one considers the acute onset, the stormy febrile course, the rapid recovery, and the excellent condition of the patient after two years, I firmly believe that we may look upon this as a case of Addison's disease recovered if not cured.

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[3] Osler's System of Medicine.

SUMMARY. The unusual features in this case are:

1. The sudden onset with pain, chills, fever and sweats.
2. Bilateral involvement of the adrenals, as manifested by the marked tumor masses palpable in both lumbar and hypochondriac regions with positive urinary findings for bilateral renal pelvic involvement.
3. The early and rapidly progressive pigmentation of the skin.
4. The rapidly developing asthenia, reaching the point of helplessness in seven days.
5. The extremely low blood-pressure coming on so early in the disease.
6. The rapidly advancing anemia; 2,240,000 red cells and 35 per cent. hemoglobin in seven days, in a previously healthy, robust young man.
7. The rapid improvement which followed when once the patient had conquered the acute infectious process which was crippling his adrenals.
8. The complete recovery of the patient and continued good health for a period of two years after his dismissal from hospital.

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REVIEWS

THE CLINICS OF JOHN B. MURPHY, M.D. Vol. IV, No. 5. (October, 1915). Philadelphia and London: W. B. Saunders Company.

THE October number of the *Clinics* presents twenty-six subjects. In many of them the reader will note repetition of comments made in similar cases. It is inevitable that repetitions become more frequent as the total number of cases grows with each volume. They do not, however, detract from the value of the publication if it is read with the idea of obtaining the opinion of the author on the minor practical points emphasized in each case presented. Dr. William B. Coley reports the disappearance of an inoperable recurrent carcinoma of the nasopharynx under treatment with mixed toxins. Dr. Murphy advocates the use of the Roentgen-ray and arsenic in addition to Coley's fluid in certain types of sarcoma. The results cited justify a measure of optimism. In the chapter on metastatic arthritis of the knee-joint, the value of autosensitized vaccines is again emphasized. G. M. L.

THE CLINICS OF JOHN B. MURPHY, M.D. Vol. IV, No. 6 (December, 1915). Philadelphia and London: W. B. Saunders Company, 1915.

THE reader of the *Clinics* will recall that Dr. Murphy has repeatedly condemned radium therapy in cancer of the mouth, and will observe with interest a footnote referring to the favorable results reported by Sticker. In contrast to the precision that characterizes the usual teaching, we note certain discrepancies concerning the question of removal of the cervical lymph nodes in the case of leukoplakic papilloma. Case teaching, of necessity, prevents full academic discussion of all the phases of a subject, and probably is of greatest value to the average reader in illustrating the methods of treatment practised by the author. For example, one observes that the importance of avoiding hand-contacting in bone work is dwelt upon; that the ether-olive oil method of anesthesia is sometimes employed; that some wounds are swabbed with 5 per cent. phenol; that the cut ends of nerves are sutured to prevent neuroma formation, and that special care is taken in suturing the skin to prevent scar formation. G. M. L.

THE CLINICS OF JOHN B. MURPHY, M.D. Vol. V, No. 1 (April, 1916). Philadelphia and London: W. B. Saunders Company, 1916.

THE most important feature of the April number of the *Clinics* is a Talk on the Surgery of Tendons and Tendon Sheaths, with special reference to the newer anatomy according to Mayer. It is rich in practical surgical suggestions. Speaking of felons, Dr. Murphy says: "To thrust a blind knife blindly into the human hand is nothing, if not criminal." "Every acute deep infection of the hand should be treated by an exploratory dissection under anesthesia and anemia." "To operate without an anesthetic is sheer brutality, surgical tyronism, unjustifiable and indefensible." There follows a case of retention cyst of the lip, with interesting comments on the histology and surgical pathology, an excellent *résumé* of the subject of cervical rib. Several cases showing lesions of the central nervous system are presented, with the keen clinical analysis of Dr. Mix. The remainder of the volume is devoted to the surgery of the extremities, illustrating the newer surgery of tendons, arthroplasties, and nailing of fractures. The volume is one of exceptional merit. G. M. L.

MAN: AN ADAPTIVE MECHANISM. By GEORGE W. CRILE, F.A.C.S., Professor of Surgery, School of Medicine, Western Reserve University. Pp. 379; 88 illustrations. New York: The Macmillan Company.

IN his latest book, Dr. Crile attempts to show that "man is essentially an energy transforming mechanism," the whole process of energy transformation being under the direction of the "kinetic system," composed of the brain, "the great central battery which drives the body, the thyroid governs the conditions favoring tissue oxidation, the adrenals govern immediate oxidation processes, the liver fabricates and stores glycogen, and is the great neutralizer of the acid products of energy transformation, and the muscles are the final converters of latent energy into motion and heat." These organs have acquired their special function by a process of ages of adaptation to the exigencies of environment.

Doubtless no one will quarrel with Dr. Crile as to his fundamental thesis: the animal body is unquestionably a perfected mechanism for the transformation of energy. All will further agree that man is an adaptive mechanism,—not only the genus man, but the individual man. The result of the adaptability of the individual to his environment is to be seen in this book, and constitutes the chief criticism of the book.

Dr. Crile is a surgeon. The surgeon is a man who must think quickly and act immediately upon his thought, for delay in Surgery may be more serious than a false move. Therefore the surgeon adapts his mode of thought to this demand upon him; as a man among men he acquires the reputation of being energetic, forceful, decisive; he settles affairs in his own mind with astonishing quickness,—and both inside and outside his profession he sometimes moves too fast. The internist has more time in which to act,—when an acute emergency arises he sends for the surgeon. The laboratory man moods and broods, and earns as justly, perhaps, the criticism that he never gets anywhere.

Dr. Crile's book will therefore appeal differently to different minds depending upon the environment to which they have become adapted. The surgeon will follow the reasoning, which is clear and logical in so far as the presented statements are concerned. The internist will not be very deeply convinced, and the laboratory man will be dumfounded.

For example, after 275 pages designed to show how man has risen to his present stage of development by a process of age-long adaptation to his nevironment, we learn that "in the pregnant state there is progressive loss of muscular power, mental efficiency and resistance to infection. Memory, reason and endurance suffer just as they do in infection or in auto-intoxication." It seems strange, indeed, that woman should have so poorly adapted herself to the process which represents the end and aim of her entire being—the procreation of the species! And this statement cannot be true without modification, for on page 281 we learn that "pregnancy in anemic, chlorotic, adynamic women sometimes transforms them and gives them added weight and energy." And on page 284 we learn, further, that "in the school of natural selection there have been evolved . . . mechanisms in the tissues of the genital tract and genital organs for protection against infection."

And so throughout the entire book the meticulous critic will find discrepancies which will prove fatal to the argument if the reader's mind has become adapted to an analytic habit of thought. In fact there are many who will question the applicability of the statement in the introduction to the problem at hand: "Like other sciences medicine has had to evolve through the three traditional stages of development; a stage of superstition and empiricism; a stage of experiment and accumulation of data; and a final stage of synthesis and coördination of facts. That medicine is well through the second stage and has entered the final stage of synthesis in which practical working principles are being formulated is evidenced especially by the increasing control of infectious diseases,"—but this evidence is by no means applicable to the condition of our knowledge of the ductless glands, as Dr. Crile seems to think. J. E. S.

STUDIES IN SURGICAL PATHOLOGICAL PHYSIOLOGY FROM THE LABORATORY OF SURGICAL RESEARCH, New York University. Edited by JOHN WILLIAM DRAPER.

THE volume comprises twenty-eight reprints which have appeared at various times in different journals. The purpose and usefulness of such a volume is as stated in the foreword by William J. Mayo—the collection and publication of the results of the investigations of a group of men, working along related lines. J. E. S.

EMBRYOLOGY, ANATOMY, AND DISEASES OF THE UMBILICUS, TOGETHER WITH DISEASES OF THE URACHUS. By THOMAS STEPHEN CULLEN, M.D., Associate Professor of Gynecology in the Johns Hopkins University; Assistant Visiting Gynecologist to the Johns Hopkins Hospital. Pp. 680; 269 illustrations. Philadelphia and London: W. B. Saunders Company, 1916.

THIS book is a *Sepulchretum* of the surgery of the umbilicus and urachus; only most of the facts here buried are derived from living patients, not from cadavers, from autopsies *in vivo* rather from *postmortem* studies as is the case in the great work of Bonetus.

Most medical men are still in the happily ignorant frame of mind in which the author of this volume found himself in 1904, when, as he tells us in his preface, he was rudely awakened to the fact that other diseases than hernia affect the umbilicus by being asked to see in consultation a patient with cancer of the umbilicus. The fact that this was an adenocarcinoma set him thinking, seeking for an explanation; and the outcome of it all is this portly volume, beautifully illustrated by Max Brödel.

Perhaps it is the very portliness of the volume, perhaps it is merely a habit of much writing acquired during its preparation, that inspired the author with the idea of condensing its contents into a preface of some three thousand words. We urgently counsel those who may contemplate, as we fear some hardy souls may, the perusal of the entire volume from cover to cover, to begin systematically with the preface. Then to follow the advice therein contained to study (not merely to admire) the illustrations of embryology; and then (but this advice is not in the preface) to lay the volume carefully away upon its shelf, to be called upon as a work of reference whenever needed—and this, we predict, will not be very often.

The plan of the work is all inclusive: embryology, anatomy; umbilical infections in the newborn; remnants of the omphalomesenteric duct; congenital polyps; Meckel's diverticulum; intestinal cysts; umbilical concretions; purulent and fecal fistulæ at the umbilicus; umbilical herniæ; umbilical tumors; patent urachus; urachal cysts—these are but a few of the chapter headings, for the volume treats *de omnibus rebus et quibusdam aliis.* Not only is the history, the pathology, the symptoms, the diagnosis, the prognosis, and the treatment of each condition given at length, but there is appended nearly to every section a long list of case abstracts, alphabetically arranged according to the author's name, which have been disinterred from former and less worthy sepulchres to be reinterred with befitting pomp and splendor in this magnificent mausoleum.

It is indeed a *magnum opus*; it is even a κτῆμα ἐς ἀεί; but we fear it will not be appreciated by the bulk of the profession as it deserves to be; for its preparation has involved immense labor, and it is an unexceptionably valuable storehouse of facts, a Sepulchretum well worthy the name. A. P. C. A.

Kurze Praktische Anleitung zur Erkennung aller Formen des Kopfschmerzes. von Oberstatsarzt Dr. Lobedank. Pp. 71. Würzburg: Curt Kabitzch.

The author has arranged in tables the various diagnostic points of every imaginable form of headache, so that by a rapid glance through the book the type of headache can be immediately diagnosed. The usual criticisms apply to this book as to all books of a similar character. J. H. M., Jr.

A Synopsis of Medical Treatment. By G. C. Shattuck, M.D., Assistant Physician to the Massachusetts General Hospital. Second edition. Pp. 185. Boston: W. M. Leonard.

This little book contains a brief synopsis of various types of treatment that the author has found efficacious in his private practice and hospital work. The methods of treatment are based upon actual pathology and are, for the most part, sufficiently complete to form the basis of therapeusis in the usual run of cases seen by the practitioner. J. H. M., Jr.

Orthopedic Surgery. By Edward H. Bradford, M.D., Consulting Surgeon to the Children's Hospital, Boston, and to the Boston City Hospital; Professor of Orthopedic Surgery Emeritus in Harvard University, and Robert W. Lovett, M.D., Professor of Orthopedic Surgery in Harvard University; Surgeon to the Children's Hospital, Boston; Surgeon-in-chief to the Massachusetts Hospital School, Canton. Pp. 416. Fifth edition. New York: William Wood & Co.

"Dictated but not read." It was not so stated in the preface, but we feel that it should have been out of justice to the Boston authors. Like the lawyer before the court, we raise many objections and trust that the judge (the reader) will sustain us in most of them.

We object to the terms "nodes" and "glands" being used in the same paragraph, and to the latter being used at all, since lymph-nodes are glands in no sense of the term; to "dorsal" being made to specify the thoracic region of the spine, for all regions of the spine are dorsal; to "tubercular" being used for the adjective tuberculous, since the former denotes any disease characterized by tubercles, while the latter specifies infection by B. tuberculosis; to a roentgenogram being referred to as an "*x*-ray"; to the term tuberculous "ostitis," since the pathology is that of osteomyelitis; to the term syphilitic ossifying "periostitis," since the pathology is that of osteoperiostitis; to the term acute "osteomyelitis" of the knee-joint, since osteoarthritis is meant; to "Wasserman" instead of Wassermann; to "Trendelenberg" instead of Trendelenburg; to the use of the obsolete and meaningless terms "sciatica" and "lumbago"; to Volkmann's ischemic contracture being termed a "paralysis," since the pathology is that of interstitial myositis; to the statement that the deep "prepatellar" bursa lies beneath the ligamentum patellæ, when the infrapatellar fatty bursa is meant; to the term "metacarpal" for the long bones of the foot; to "metatarso coneiform" for metatarsocuneiform; to the location of Chopart's joint at the hip-joint, viz., "the limb rotating at the midtarsal articulation at the hip-joint'; to "fixed" when flexed is meant; to the dubious statement "The patella lies farther outside than it should do, and the knees are laterally loose," and to this one, "Treatment should be continued not only until the bone has become not only sufficiently strong . . . but to withstand."

Offsetting the above is the rare correct use of the term "cast" as the reproduction of an object in solid form, instead of the prevalent perverted use to denote the mold from which the cast is made.

Regarding bursitis we believe that ablation is preferable to mere incision; and that so long as trochanteric bursitis and housemaid's knee are mentioned miner's elbow should also be referred to.

The most practicable position in case of ankylosis is given for every joint with the exception of the wrist.

We believe that antiseptic bone-wax, pig's bladder and ox's peritoneum (Cargile membrane) are of historical importance alone at the present time: in reference to Cargile membrane, for example, it was shown so long ago as 1905 by Craig and Ellis that until absorbed this material acts as a foreign body, and therefore is an irritant; we are glad to see, however, that bismuth paste is not recommended for the healing of bone-sinuses.

The whole subject of cystic bone disease is dismissed with the statement "echinococcus cyst and "aneurism" must be mentioned as other possibilities."

In the single paragraph devoted to gout practical value could be added by mentioning the three diagnostic features of Brugsch, and especially in the acute stage the differentiation from suppurative infection, for the error of incising gout in mistake for the latter has not yet been banished from the modern practice of medicine and surgery; the association of great pain with slight or no fever is a point of diagnostic value. It may be said here that there should be a greater recognition of medical diseases—especially diagnoses—throughout the work.

Instead of treating the hemarthrosis of hemophilia by gelatin by mouth, the more modern, more rational, and more promising method of intravenous medication by human blood serum should be used.

An unfortunate feature of orthopedic works as a class is that descriptions of operative technic are too brief for comprehension and too inadequate for practical application.

The revolutionary changes in orthopedic surgery wrought by the ever widening application of the autogenous bonegraft—especially the many clever applications carried out by Albee—are dismissed in one paragraph on "Bone Grafting." It is of vital importance that a modern treatise on orthopedic surgery should give a somewhat detailed description of bonegraft work. Thus, examples to hand are the correction of clubhand by a bonegraft to supply the missing radius and of clubfoot by bonegraft-widening of the split scaphoid; others have been referred to above, and the rest are too numerous to mention here.

The index should be overhauled: it does not contain even the term "arthroplasty."

The best portions of the book are those dealing with the employment of braces, deformities of rickets, lateral curvature of the spine, and infantile paralysis, in which the use of orthopedic apparatus is clearly described.

For the rest we find a mere catalogue of orthopedic diseases written in the loose medical vernacular of the day. On the whole we are disappointed, for, in keeping with the eminence of the authors, we expected more — especially of gleanings from their mellow personal experience. P. G. S., Jr.

THEORY AND PRACTICE OF BLOODLETTING. By HEINRICH STERN, M.D., LL.D.; Visiting Physician, St. Marks Hospital; Consulting Physician, Methodist Episcopal (Seney) Hospital; State Hospital at Central Islip. Pp. 264; 94 illustrations. New York: Rebman Company.

THE author, anticipating a revival in bloodletting, sets forth in a systematic manner its progress from the most ancient times to the most recent clinical and experimental investigations.

While conservative in his views, and in no way accepting the procedure as a panacea, he warmly advocates its conditional application and sets forth clearly the indications for, and advantages of, its employment in various diseases.

The book is divided into two parts, the first of which includes the history of bloodletting. Following this the physiological effects are adequately discussed and then the technic is presented in detail, with many illustrations of instruments.

The second part consists of a clinical resumé of the numerous diseases in which bloodletting has been utilized as a therapeutic measure. It is divided into sections, the first dealing with diseases of the respiratory organs, the second with circulatory disturbances, the third with uremia, etc., a brief reference being made to a large number of diseases.

A few of the author's cases are cited as illustrations of the actual advantages derived, especially in the circulatory disturbances. His views are interspersed with those of many others. Evidently he has enjoyed a wide experience with this therapeutic measure and is, without doubt, a keen enthusiast.

The book is of especial value to one interested in therapeutics. While many of the facts might be ascertained from text-books on medicine and surgery, many more and valuable ones are to be found in this volume. A. H. H.

THE TRYPANOSOMES OF SLEEPING SICKNESS; BEING A STUDY OF THE GROUNDS FOR THE ALLEGED IDENTITY OF T. BRUCEI WITH THOSE CAUSING DISEASE IN MAN IN NYASALAND. By G. D. MAYNARD, F.R.C.S., E., Statistician and Clinician to the South African Institute for Medical Research. Pp. 39; 26 charts. Johannesburg: W. E. Horter & Co., Ltd.

THE author attempts to prove that the trypanosome causing human disease in Nyasaland is not identical with T. brucei, thereby differing with the Sleeping Sickness Commission of the Royal Society, which recommended the diminution of wild game in fly areas on the basis of such identity. He appears to have succeeded in this by analyzing (1) length—measurements, (2) geographical distribution, (3) pathogenicity for various animals, (4) carriers, (5) serological reactions, from data gathered from several sources but does not appear to have done any experimental work personally. He also advances several hypotheses to explain the greater virulence of Nyasaland sleeping sickness over the more northern ones.

F. D. W.

THE PSYCHOLOGY OF THE KAISER. A STUDY OF HIS SENTIMENTS AND HIS OBSESSION. By MORTON PRINCE. Pp. 112. Boston: Richard G. Badger.

THIS little essay is a study of the German Emperor from the point of view of his subconscious self, the dominant trait of which, according to Prince, is a phobia, a fear of democracy for himself and his House.

The author discusses William II's "Divine Right Delusion," his sentiment of self-regard, his extraordinary arrogance and vanity, and his desire to conquer the world. T. G. M.

AN INTRODUCTION TO BACTERIOLOGY FOR NURSES. By HARRY W. CAREY, A.B., M.D., Former Assistant Bacteriologist, Bender Hygienic Laboratory, Albany, New York; Associate in Medicine, Samaritan Hospital, and City Bacteriologist, Troy, N. Y. Pp. 144; 17 illustrations. Philadelphia: F. A. Davis Company.

THE book has been well planned, and contains enough information to more than properly equip the average nurse. The author has appreciated the necessity for simple language, as expressed in the preface, and so far as verbiage is concerned, has succeeded, but some of the sentences might be reconstructed to advantage with the idea of making their meaning plain without second reading. To the reviewer's mind, its seventeen illustrations are far too few for a beginner's book, and some of them might have been better selected. The blank leaves for long-hand notes are valuable, and its very low price is an important feature for the class of students for which it is designed. Taken all in all it is a very valuable little book. F. D. W.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
W. S. THAYER, M.D.,
PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,
AND
ROGER S. MORRIS, M.D.,
FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

The Protective Ferments of the Body.—This article by WALLIS (*Quart. Jour. Med.*, 1916, ix, 138) is essentially a critical analysis of the principles of the articles which have appeared either in support or in refutation of the much discussed Abderhalden reaction. He points out clearly that the subject under discussion is of the greatest importance since the elucidation of some of the many problems of immunity which still await solution are probably wrapped up in doubt. The physiological basis upon which Abderhalden devised his test is clearly stated and followed by a description of the two chief methods for performing the reaction, namely, the optical method and that of dialysis. From a study of the application of the reaction to the diagnosis or pregnancy, diseases of the internal glandular system, dementia precox, and some of the infectious diseases, the author comes to the conclusion that the principles of the method as laid down by Abderhalden do not coincide with the experimental data, and hence other explanations must be sought. He points out with great clearness the fact that this test, like many others, was at first claimed to be infallible as an exact method and even before the fundamental principles upon which it was based had been conclusively proved. The reaction, however, has been of the greatest value from a scientific point of view, for the entire theory of the Abderhalden reaction goes back to the root of the problem of immunity, namely, the cell itself and its protein constituents. As a result of this, there has been a great advance in our conception of immunity and in our knowledge of colloidal chemistry and ferment action, so much so that they may be brought into line in the near future in a solution of the many problems of physiology, and clinical medicine.

Complement-fixation in Varicella.—Kolmer (*Jour. Immunol.*, 1, i, 51). The author points out that the object of this investigation was to determine whether antibodies could be detected in the blood serum of persons actively infected with varicella and after recovery by means of complement-fixation tests. The usual Wassermann reaction technic was employed in which antigens were used made from the extracts of contents of the vesicles and crusts of this disease. The net results of the study were that complement absorption does occur in the sera of varicella patients, but the reactions in most cases were slight, never outspoken. Negative reactions with all antigens used were observed in the sera of adult persons who had had varicella in childhood. In all such people the Wassermann reaction was negative in the absence of syphilis. Cowpox and variola antibodies did not absorb complement when mixed with varicella antigens, hence it can be shown that though antibodies are formed, the percentage of positive reactions, particularly when the degree of complement absorption is small. The author is of the opinion that a more delicate technic would probably yield a better percentage of positive reactions, but the danger there would be in the possibility of obtaining non-specific absorption of complement.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Melano-epithelioma.—Broders and MacCarty (*Surg., Gynec. and Obst.*, 1916, xxiii, 28) say, from a study of 70 cases from the Mayo Clinic, that the so-called "melanosarcoma" should be called properly a melano-epithelioma when such a condition arises in the skin. The condition arises as a migratory hyperplasia of the basal (regenerative or germinal) layer of the skin and invades the subcutaneous tissues and distant organs as pigmented and non-pigmented oval, spherical, or spindle cells, all of which cells are frequently found in the same specimen or even in the same microscopic slide. The evolution of such neoplasmata in regenerative cells corresponds to the evolution of cancer in the skin, mammary gland, prostate gland, and stomach. The alveolar arrangement of cells in this series shows no evidence of any relation to vascular endothelium. The condition is one of middle life, although it may be found from childhood to old age. An attempt at determination of the exact duration of the condition from its onset to a fatal termination has failed in this series. There is no specific region of the skin which seems especially predisposed to the development of melano-epitheliomata unless it is on the lower extremities, which in this series form the greatest frequency of location. Nevi certainly predispose to the development of the condition. Metastasis is usually to the regional lymphatic glands. From an economical or practical stand-point melano-epitheliomata which arise in the skin have a high mortality. Melano-epitheliomata or melanosarcomata arising in the eye have much better prognosis than melano-epitheliomata arising in the skin. From a therapeutic stand-point the pathological history of melano-epithelioma clearly points to the necessity of an early diagnosis and a radical removal of the primary lesion and regional lymph glands. From a prophylactic stand-point, pigmented areas of the skin, such as warts and nevi, should be removed when these are in locations which are or have been subjected to injury.

A Contribution to the Etiology of Cancer of the Esophagus and Stomach.—LERCHE (*Surg., Gynec. and Obst.*, 1916, xxiii, 42), from an extensive study of the literature, found that cancer of the esophagus and stomach is peculiarly prevalent in the temperate climate zone. The relative frequency with which cicatricial strictures from swallowed corrosive fluids occur in the various parts of the esophagus increases from above downward—in other words, the widest parts of the esophagus—are the most frequent sites of such strictures, and for physiological reasons. The distribution of cancer in the esophagus corresponds to that of the cicatricial strictures from swallowed corrosive fluids, and in all probability for the same physiological reasons. Any part of the esophagus and stomach may be the starting-point of cancer with the exception of the pyloric sphincter, which rarely seems to be the primary focus. The organ immediately beyond, namely, the duodenum, is practically immune from cancer. The reason for the two latter phenomena is probably that the ingests do not reach the pyloric sphincter until they are properly modified. In view of the foregoing conclusions, it seems logical to look to the ingesta of civilized man for the source of chronic irritation, which leads to malignant changes of the esophagus. The supposition that swallowed fluids after emanating from the cardia are directed along the "gastric gullet" to the prepyloric region is strongly supported by the fact that the cicatrices from smaller quantities of swallowed corrosive fluids are usually found along this path. Seventy-nine per cent. of cancer are found along this path—the cardia, the "gastric gullet," and the prepyloric region. As cancer of the stomach follows the "highway of the fluids," it seems logical to assume that ingested fluids in particular may be responsible. Alcohol and other irritating fluids probably play a part, but in the opinion of Lerche, "hot fluids" so universally taken throughout the temperate zone, in the form of coffee, tea, soups, etc., and giving rise to chronic irritation, is the main predisposing cause of cancer of the esophagus and stomach. Cancer of the esophagus occurs less often in women than in men, because women drink more slowly and take smaller swallows, which pass quickly through, thus saving the esophagus, while the less resisting mucosa of the stomach, where the fluids come to a stop, is more equally exposed in both sexes. The fact, therefore, that the ratio of cancer of the esophagus in men and women is 3.5 to 1, while cancer of the stomach occurs with almost equal frequency in both sexes, points strongly to "hot fluids" as the important predisposing cause. This is further substantiated by the results of a comparison between the cancer statistics and the habits of the people in the north and south of Europe, by the relative freedom from cancer of the esophagus and stomach enjoyed by the aborigines of hot climates and the extremely rare occurrence of cancer of the stomach in animals

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Rupture of Bladder Associated with Fracture of the Pelvis.—Quain (*Surg., Gynec. and Obst.*, 1916, xxiii, 55) reports a case of this kind and collected 126 similar cases, from the literature of each of which he gives a brief abstract. In the majority of these cases it was found that a spicule of bone had perforated the bladder. Most lacerations thus caused were extraperitoneal and several were multiple. With the exception of the instances where a foreign body had entered the pelvis from without (gunshot, etc.) only four cases in which a lacerated bladder communicated with the outside have previously been described. With two or three exceptions the treatment has evidently been limited to the application of a bandage around the pelvis, after possibly some adjustment of the fragments. The treatment has often been complicated seriously by infection and necrosis of the bone. Of the 127 cases now reported, 34 "recovered," a total mortality of 74 per cent. But of these were 83 cases, reported before 1890, with a mortality of 72, or 86.7 per cent. Of 44 cases since 1890, *i. e.*, during the period of aseptic surgery, 23 lived—a mortality of less than 48 per cent. Since 1905 the mortality has been reduced to 38 per cent. The total mortality in all varieties of ruptured bladder which have been treated surgically since 1900 is less than 25 per cent. This shows in figures the extreme gravity of the lesions under discussion, and indicates that fracture of the pelvis is the most serious complication of a ruptured bladder. In point of morbidity, Quain believes with Fuller that most patients with extraperitoneal rupture of the bladder are left seriously invalided for life.

The Operative Treatment for the Disabilities and Deformities Following Anterior Poliomyelitis as Practised at the Hospital for Ruptured and Crippled during the Past Three years.—Wallace (*Am. Jour. Orthop. Surg.*, 1916, xiv, 400) presents a tabulated study of 666 cases divided into eleven groups, with particular reference to the special condition and the treatment employed, and all of these into three classes with reference to the results obtained, the successful, the improved, and the failed. He says that nearly one-third of the operations in the foregoing tables would have been unnecessary if the patients had received proper brace attention. The Soutter operations for contractures about the hip have been most beneficial. The transplantation of an active hamstring tendon, when both were normal, to the attachment of the paralyzed quadriceps extensor tendon has so improved the power about the knees that braces have been discarded. Arthrodeses operations for paralytic deformities in children have been of little value. The grooving of the tibialis anticus tendon into the anterior surface of the tibia and transplanting the extensor propius hallucis tendon to the calcaneoscaphoid ligament for equinovalgus deformity has been helpful. The most satisfactory operation for calcaneus, calcaneovalgus, and dangle-foot deformity has been the typical

Whitman. The backward displacement of the foot accompanied with astragalectomy are the essential features of this operation, and they have been utilized to great advantage in all types of paralytic foot deformities. When successful a firm basis for standing and walking has been secured, and after a few months of supervision the patients have been able to walk without artificial aid, thus probably stimulating the growth of the paralyzed extremity. The improved circulation so increased the warmth of the feet that the tendency to chilblains was lessened.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

Hay Fever and Certain other Local Anaphylactic Phenomena Referable to the Respiratory Mucous Membrane.—Hichens and Brown (*Jour. of Lab. and Clin. Med.*, 1916, i, 457) summarize the principles of the present-day treatment of hay fever. They divide the treatment into measures to be taken two to three months previous to the hay-fever season and measures to be taken immediately to control the acute attack. When the patient can be studied beforehand a survey of his habitual surroundings, and skin tests should be made with pollens of such plants that may be considered as having a possible connection with the anaphylactic phenomena. If the attack has already started, treatment should be begun at once with a vaccine representing the pollens most likely to be responsible for the attack. If the treatment does not give entire relief, an exact diagnosis may be made quite independently of the treatment. Hichens and Brown report 63 cases of hay fever treated with pollen vaccines, of which 18 were complicated with asthma; of these 18, 11 were entirely relieved, 3 were considerably relieved, 1 was not relieved, and 3 were not reported. Of the remaining 44 cases, 17 were entirely relieved, 18 were considerably relieved, 4 were slightly relieved, 2 were not relieved, and 3 were not reported. One patient, who was treated in summer and autumn for two years, was apparently cured. The two vaccines used by the authors were, in the spring, a mixture of pollens from red-top timothy, rye, and orchard grass, and, in the fall, the pollen of ragweed alone. They call attention to the fact that in every case the possibility of a concurrent bacterial infection must be taken into account. Cases that present especial difficulty in treatment are those that suffer from hay fever from earliest spring to latest autumn.

Some Observations on the Treatment of Hay Fever.—Wilson (*Laryngoscope*, 1916, xxvi, 937) reports 26 cases of hay-fever treated by the injection of various pollen extracts and 22 cases treated by calcium chloride. He says that the desensitization of hay fever patients by means of specific pollen solutions will materially relieve a small percentage of them if treatment is begun early enough. Pollen solutions for therapeutic use should be prepared and used with great care and understanding. When improperly prepared or used there is danger of serious if not fatal reactions. Multiple sensitization is a frequent phenomenon in hay fever subjects, and its existence may account for many failures in the treatment by means of pollen solutions. The treatment of hay fever by means of calcium salts rests largely on empirical observations, but from the limited data at hand, if the doses are sufficiently large and prolonged through a more or less extended time, a large percentage of patients will receive material benefit. It is possible that vernal cases yield more readily than autumnal cases. The administration of calcium salts is without danger to the patient and may be undertaken by any intelligent physician. It requires neither a careful laboratory technic nor any special knowledge for its employment.

The Cause, Treatment, and Prevention of Hay Fever.—Sheppegrell (*Med. Record,* 1916, xc, 95) says that the class of plants whose pollen may cause hay fever are practically all common weeds, and are very numerous and generally distributed. They all have abundant pollen and are wind-pollinated, that is, the process of fertilization is effected by the pollen being borne on the wind. These weeds are without attractive color or fragrance, and in the process of wind-pollination their pollen is very widely distributed. The author says that the elimination of pollen in the immediate vicinity of the patient is most important. Great relief to patients suffering from hay fever is observed when the hay fever weeds in close proximity are cut down, although, in order to be more completely effective, the efforts against hay fever weeds should be reinforced by proper legislation. Inasmuch as the common hay fever weeds are pests to the farmer, such legislation will serve a twofold purpose. The author discusses the treatment of hay fever by the injection of pollen extracts, calcium chloride, etc., and although adding nothing new, is a firm believer in the proper administration of pollen vaccines. Only the pollen should be used for vaccine, to which the patient reacts by the nasal, conjunctival, or skin reaction. The injection of a wrong vaccine may cause the patient to become sensitive to the pollen from which the extract is prepared. In some cases the effects of hay fever are due not only to the absorbed pollen protein but also to the action of microörganisms resulting in an inflammation of the nasal mucous membrane due to its lowered resistance. Finally, immunity to hay fever even in hay fever patients does not mean that the patient is not inhaling pollen but that the amount is not greater than can be neutralized. Hence, diminishing the source of pollen supply is a very important if not the most important part of proper therapy. Sheppegrell says that in New Orleans local legislation against the hay fever weeds has caused a marked reduction in the number of hay fever cases.

The Intracranial Injection of Salvarsanized Serum.—Wardner (*Am. Jour. Insanity,* 1916, lxii, 643) reports a series of fourteen patients treated by the above method. Of this group of fourteen patients, five improved sufficiently to be able to go back to their work, and to date have remained well for from seven to eleven months. At the end of eleven months one of these patients had a relapse, which responded immediately to further treatment. Then other patients, with well-developed disease, have improved sufficiently to be able to do a certain amount of work about the hospital. Three others have shown fairly marked physical and mental improvement but cannot as yet be trusted at large. Two cases have died, one of which had previously shown a well-marked improvement. Two cases have shown no improvement. Both mental and physical improvement has generally been observed after the second or third operation, and has followed so closely on the treatment as to practically preclude the idea of coincidence. The maximum amount of improvement has occurred, as a rule, after six or seven treatments. Wardner believes that intracranial injections are without danger as shown by the fact that 102 have been performed without untoward results. The cases reported were not selected, and represent general paresis in a moderately advanced stage in most of the cases treated. The clinical diagnosis of general paresis was supported in every case by the laboratory findings. When pupillary changes existed no marked effect has been noted after the treatment. Reflexes, when previously exaggerated, show a tendency to become less so. Coördination and speech have been improved in all. The Wassermann reaction in the blood has been rendered negative in 6; reduced in intensity in 4; unchanged in 3, and not taken in 1. The Wassermann in the spinal fluid has been rendered negative in 2; reduced in 6; not retaken in 2; and unchanged in the rest. The cell count has been reduced to below 10 per c.mm. in 12; not retaken in 2. Wardner says that it is impossible to state what the final outcome of these cases will be, but believe that if cases of early general paresis, in which the actual destruction of brain tissue might reasonably be supposed to be slight, could be thoroughly treated, much might be done to control the future progress of this condition.

The Treatment of Paresis.—Evans and Thorne (*Am. Jour Insanity*, 1916, lxxii, 624) have treated 15 patients suffering from paresis with salvarsan and neosalvarsan; 14 of these patients were treated by the intraspinous method of Swift and Ellis and 1 by the intraspinous and intracranial methods combined. With the latter method two intracranial treatments were given at four weeks' interval, together with three intraspinuous injections. The largest number of intraspinous injections given to one individual was ten and the smallest number three. Three of these patients showed distinct mental and physical improvement; 5 showed physical improvement only; 2 died during the course of treatment; 2 died ten and thirteen months, respectively, after treatments were discontinued; the remainder showed no improvement whatever. Of the 3 who showed mental and physical improvement 1 was discharged and still remains in good physical and mental condition, having returned to work. One showed the first signs of improvement three months after receiving the last treatment. The third died with convulsions ten months after treatment. The number of treatments given to each patient was insufficient to reduce the intensity of the Wassermann reaction either in the blood or the spinal fluid. The improvement observed following the treatment may be seen in the same number of paretics who have received no special treatment. The authors believe that the amount of salvarsan which can be introduced safely into the central nervous system is too small, and the intervals are too long between the treatment, to be of great value in moderately advanced cases. The intracranial method seems to be unecessary according to the authors. They believe that the same result can be obtained by the intraspinous method.

The Treatment of Paresis by Intraventricular Injections of Diarsenolized Serum.—Knopp (*Boston Med. and Surg. Jour.*, 1916, clxxv, 24) says that in a fairly large experience with the treatment of syphilitic affections of the central nervous system by intraspinal injections of salvarsanized serum by the Swift-Ellis method and its modifications he has been impressed that in no other way can such consistently good results be obtained. This opinion is reached from the study of about 500 injections, on over 100 patients. His experience, like that of most observers, has lead him to believe that the action of salvarsan and its substitutes, neosalvarsan and diarsenol, is most pronounced when it is exerted most directly upon the spirochete. He has seen tabetics who could stand only by the support of two nurses when treatment was first begun, who after a few injections could walk several miles with an approximately normal gait. He has seen patients completely paraplegic, with total loss of control of the bladder, who acquired normal sensibility and reflexes after three injections. Such brilliant results, however, have not been observed in cerebral cases. In view of the necessity to secure a more direct influence of the remedial agent in cerebral cases, Knapp has tried the injection of diarsenolized serum directly into the lateral ventricles. Knapp prefers to do this operation under general anesthesia, and considers the operative procedure fairly safe and the risks apparently slight. He says that his experience is too limited to permit any definite conclusions, but that changes in the physical signs—the return of the knee-jerk, the return of normal pupillary reactions—are not often seen in paresis under any other treatment. These facts, taken in conjunction with the apparent general improvement of the patients, encourage him to continue with this method of treatment.

Intraspinal Injections of Bichloride of Mercury.—Hunt (*Boston Med. and Surg. Jour.*, 1916, clxxiv, 788) had previously reported 40 cases of spinal syphilis treated by the intraspinous administration of mercurliaized serum, and 5 cases treated by the direct intraspinous injections of bichloride of mercury. Since that time he has treated 12 additional cases by the direct administration of bichloride of mercury into the spinal fluid. These 12 cases consisted of cases of general paresis, tabes, taboparesis, hemiplegia, optic-nerve atrophy, and 1 case of brain syphilis with complicating hemiplegia. They were given either $\frac{1}{64}$ or $\frac{1}{30}$ of a grain of bichloride of mercury at such intraspinous injection. The injections were approximately at intervals of two weeks. The patients were at the same time being given mixed antisyphilitic treatment. In a few of these patients it was not possible to obtain definite results but in the large majority distinct improvement was manifest. Hunt believes that the administration of bichloride of mercury directly into the spinal fluid gives practically the same results as the administration of mercurialized serum. It has the advantage over the latter of simpler technic, shorter methods, and easier administration, with less opportunity of infection. Both methods, that of the mercurialized serum and that of the bichloride directly injected into the spinal fluid, can be considered as valuable substitutes for the administration of salvarsan. Certainly no ill results can accrue from the direct intraspinous injection of $\frac{1}{50}$ of a grain of bichloride of mercury in syphilis of the nervous system. Whether the results will be as permanent as the latter remains to be seen. In no instance was any change manifest in the reflexes, but change was evident in the tremors, in the pains, in the spinal fluid count, and especially in the general condition of the patient.

The Treatment of Arthritis by the Intravenous Injection of Foreign Proteins.—Miller and Lusk (*Jour. Am. Med. Assn.*, 1916, lxvi, 1756), after observing that similar results were obtained in the treatment of typhoid fever by the intravenous injection of foreign protein solutions as by the injection of typhoid vaccine, tried the intravenous injection of a foreign protein for the treatment of different forms of arthritis. They used for this purpose doses of 2 c.c. of a 4 per cent. proteose solution. The patients reacted by a chill, rise in temperature, and varying leukocytosis. The day following the injection there was a moderate but distinct improvement in the joint symptoms. Later on, because of a limited supply of proteose, the authors substituted typhoid vaccine for the proteose. The reaction following the injection was the same as when the vaccine was given to a typhoid patient except that leukocytosis was much more marked, in two instances reaching 52,000. The degree of leukocytosis was dependent in a measure on the acuteness of the infection. When a patient received daily injections there was a gradual lessening in the duration of the chill, and finally the patient failed to react with a chill and the febrile reaction following the chill grew progressively less. In 3 of 10 cases of acute articular rheumatism, immediately following a single intravenous injection of 150,000,000, the fever terminated by crisis, the joint tenderness began to disappear, and within from twelve to twenty-four hours the joints were apparently normal. In these 3 cases the results were permanent. All of the 7 remaining patients were very much benefited following a single injection, but the results were either not permanent, or soreness still remained in some of the affected joints. Three or four injections, however, sufficed to relieve all symptoms. Some of the patients had relapses which yielded promptly to further treatment. Results quite as satisfactory were obtained in 6 cases of subacute arthritis of from three to nine months' duration. One patient with chronic arthritis of three years' duration received considerable relief after five injections. Results were even more striking in 8 cases of chronic gonorrheal arthritis of from two months' to three years' duration. None of these patients failed to receive decided benefit. On the other hand, patients with acute gonorrheal arthritis were only moderately benefited. The authors say that they do not know whether or not further experience will show that this method of treatment is of value as a therapeutic agent but that it at least gives further evidence of the non-specificity of vaccines. It does not, however, involve the specificity of vaccines for preventive purposes.

The Use of the "Karell Cure" in the Treatment of Cardiac, Renal, and Hepatic Dropsies.—Goodman (*Arch. Int. Med.*, 1916, xvii, 809) has employed the Karell diet in cases of renal, cardiac and hepatic edema with very favorable results. He reports a number of illustrative cases with charts of the weight, blood-pressure, urinary excretion, and sodium chloride excretion in some of the patients on this diet. Favorable effects are seen more constantly in those cases which are best termed myodegeneratio cardis, that type of cardiac disease seen in senility, emphysema, chronic alcoholism, and in cachectic states. In 60 per cent. of this type of case, improvement is seen. Valvular disease is defined in about 43 per cent. of cases, arteriosclerosis in 33 per cent., and, according to Wittich, in nephritis only 14 per cent., a percentage below that in the author's cases. Under the combination of rest in bed and the Karell diet the pulse assumes first, a better quality, and later becomes less irregular and less frequent. Blood-pressure in general is lowered particularly in cases of renal hypertension. Goodman has avoided as far as possible any indication in connection with the Karell diet but in some cases relief is needed more rapidly than is possible with the Karell diet alone. Digitalis, theocin, camphor, strophanthin, and caffein seem to act especially well when combined with the Karell diet. In a number of cases when these remedies are used alone, little or no benefit is obtained, but when combined with the Karell diet, a striking and prompt improvement results.

A Pharmacological and Clinical Study of Papaverin.—Macht (*Arch. Int. Med.*, 1916, xvii, 786) writes concerning papaverin which is one of the principal opium alkaloids in point of both quantity and pharmacological interest. One of the striking facts shown by the experiments of Macht is the peculiar action of papaverin on the circulation, promoting the coronary circulation, lowering the arterial blood-pressure, and stimulating the heart. These effects suggest its use in angina pectoris and in cases with hypertension. Macht also found that papaverin had a distinct stimulating effect on respiration which would suggest its use in cases where depression of the respiratory center is not desirable. Papaverin has considerable analgesic power and it may be used as a substitute for morphin in cases where codein is not effective. Finally, relaxation, often to a considerable degree, is produced on all smooth muscle structures. These effects, together with its comparatively low toxicity, suggested its employment for therapeutic purposes. Macht cites a number of clinical observations which are distinctly favorable, and he hopes that his experience with papaverin will stimulate further observation to determine its exact therapeutic value.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Management of Ovarian Tumors Complicating Pregnancy, Labor, and the Puerperal State.—BEACH (*Am. Jour. Obst.*, June, 1916) reports the case of a multipara in labor, the fetal head at the pelvic brim, and a contraction ring developed, but the descent of the head prevented by an ovarian tumor in Douglas's cul-de-sac. An attempt was made under ether anesthesia with the patient in the knee-chest posture to push the tumor up out of the way, but neither tumor nor fetal head could be safely dislodged. Accordingly the abdomen was opened, the lower uterine segment found greatly thinned, and a right-sided ovarian tumor present. An attempt was again made to draw the tumor up out of the pelvis while an assistant pushed the head up from below. This failed and the pedicle of the tumor began to tear. A trochar was then introduced into the tumor and a small amount of mucilaginous material was removed, but not sufficient to lessen the size of the tumor. The head was then pressed upward by the hand in the abdomen while an assistant pushed the tumor up from below. This was successful and the head of the child came into the pelvic brim and was delivered by forceps. The tumor was then removed and the stump covered with peritoneum, and the placenta pressed out by the hand grasping the uterus within the abdomen. The abdomen was then closed. Mother and child made a good recovery. In a second case three and a half months pregnant, there were several tumors in the pelvis and at the pelvic brim. These were bilateral. On opening the abdomen it was found that both had undergone torsion and both were removed. The patient recovered from the operation and aborted. The writer believes that in cases such as his first, one should avoid opening the uterus through fear of infection, especially if the membranes have long been ruptured, and repeated examinations have been made.

Posterior Dislocation of the Lower Humeral Epiphysis as a Pelvic Injury.—TRUESDELL (*Am. Jour. Obst.*, June, 1916) contributes a paper upon this subject well illustrated, giving his experience in 17 cases of this sort. The roentgen-ray pictures make the article very clear. He finds that when the arms become extended in breech cases, forcible efforts to bring them down may fracture the shaft of the humerus, or dislocate the lower humeral epiphysis. Under these circumstances the arm will hang limp at the side. Fracture of the humerus is indicated by false point of motion at the center of the shaft below the insertion of the deltoid muscle where fracture of the shaft of the humerus always occurs in the newborn. There is also dislocation of the lower epiphysis of the humerus where one can eliminate fracture of the shaft by the absence of a false point of motion at the center; but where there is abnormal motion backward and forward at the elbow when the forearm is held at a right angle to the arm, distinct crepitus may be present with either condition, and this may easily suggest the false diagnosis of fracture. The replacement of the dislocated epiphysis should be attempted as soon as possible. Traction should be made upon the arm and the forearm extended, and at the same time pressure from behind forward is applied over the dislocated epiphysis. When this is reduced the forearm is flexed to an acute angle, and a Velpeau bandage applied for three weeks. As a rule the functions of the arm are not in the least disturbed, and a good result is obtained often without a complete reduction of the dislocation.

Spontaneous Rupture of a Pregnant Uterus Followed by Little Disturbance.—Cherry (*Am. Jour. Obst.*, June, 1916) reports the case of a multipara, aged thirty-five years, admitted to hospital eight months pregnant. The day before she began to have cramp-like pains in the lower abdomen a spontaneous rupture of the membranes occurred and a diagnosis of false labor was made. Twenty-four hours later the patient came to the hospital. She stated that she had felt no movements of the child for a week. She had moderate dyspnea with slight cyanosis and some increase in pulse and respiration. On examination pregnancy was eight months, the fetus apparently presented by the breech. The head could not be felt in the upper abdomen. No fetal heart could be heard, the cervix was closed, and an irregular soft mass was movable above the pelvic brim. The patient's chief complaint was of dyspnea on lying down. The heart and lungs were normal. It was decided to introduce a dilating bag so as to hasten the development of labor. On the following day labor not having developed, section was performed. On opening the abdomen there was free blood in the peritoneal cavity, with the fetus and the placenta among the intestines. The fetus was dead, and an anencephalic monster. The uterus was well contracted and showed a longitudinal tear on its anterior and lateral walls, extending from the junction of the fundus and lower segment to the right broad ligament. On disturbing the tissues there was considerable hemorrhage from the uterus. Hysterectomy was performed followed by the uninterrupted recovery of the patient. The case is interesting, but unfortunately a minute examination of the uterine tissue was not made.

Induction of Labor Terminating in Death from Infection by the Gas Bacillus.—Cherry (*Am. Jour. Obst.*, June, 1916) reports the case of a negress, aged thirty years, a multipara. When admitted to hospital she had felt no fetal movement for two weeks. Heart sounds could not be heard. Pregnancy was seven and a half months. The patient was kept under observation for two weeks, and as the uterus showed no signs of expelling the fetus, labor was induced. This was done by introducing a dilating bag, as the cervix was hard and rigid from previous lacerations. To introduce the bag it was necessary first to dilate the cervix by instruments; antiseptic precautions were carefully observed, and twenty-four hours after the bag was introduced, as no labor pains had followed nor was there sign of dilatation, the bag was removed and larger introduced, to which a weight was attached. This was followed by no result for sixteen hours, no pains developing, nor did the cervix soften or dilate. She then had fever, nausea and chill, and died suddenly after an attack of severe nausea and vomiting, forty-eight hours after the introduction of the first bag. Twelve hours after death her body had increased three times its natural size. A partial autopsy showed a dead fetus in the uterus, and smears revealed typical Bacillus aërogenes capsulatus.

Bleeding Nipples.—Lewis (*Surg., Gynec. and Obst.*, June, 1916) reports 6 cases of patients having this condition. The discharge varied from a serous to a bloody fluid, and the pathological condition present was that described as cystadenomata. By some the process is considered non-malignant; by others, a form of cancer. In some it was possible to remove the cystic portion of the breast only, while in others the entire glands were sacrificed. Some of these patients had given birth to children and had nursed them, while others had never been pregnant. The element of pregnancy does not seem to be important in the case. In some there was no tumor, while in others tumor was distinctly present. When in doubt concerning a malignant condition, it is better to sacrifice the breast than to run the risk of its subsequent development.

Pyelitis of Pregnancy.—Danforth (*Surg., Gynec. and Obst.*, June, 1916) contributes a paper upon this subject and describes an interesting case of a woman four months pregnant, with right-sided pyelitis, with severe pain over the right kidney. On catheterizing the ureters, the catheter passed up the left ureter easily, followed by the flow of perfectly clear urine; in the right ureter the catheter was blocked about 10 c.c. from the bladder. Upon turning the patient upon the left side so that the uterus should gravitate away from the ureter, the catheter passed on into the pelvis of the kidney without difficulty, and turbid urine began at once to flow. Evidently the pelvis of the kidney had been considerably distended. The patient was very much relieved by the catheterization. To determine what relation there is between bacteria present in the bladder in normal pregnancy, and pyelitis, observations were made and 50 cultures were taken from urine secured under antiseptic precautions. From these 50 cultures, 32 showed a pure growth of staphylococci, 2 a pure culture of colon bacillus, 3 gave both germs, and 13, none. The colon bacillus then was found in pure culture or mixed with staphylococci in 5 cases. Another series were examined by catheterization under very careful antiseptic precautions. In 14, 8 cultures gave pure growth of staphylococci, 4 were negative, and 1 doubtful. When urine is obtained by the uretral catheter in cases of the pyelitis of pregnancy, the colon bacillus is found in pure culture. Evidently the germs are frequently present in the bladder of the pregnant patient although she may seem to be in excellent health. While in many cases the infection may originate in the bladder, in most cases it must be considered as coming through the blood.

Thymus Death.—Falls (*Surg., Gynec. and Obst.*, June, 1916) reports the case of a primipara with normal labor at full term ending in thirty-six hours. Two hours after delivery the child breathed badly and was cyanotic. Two hours later the symptoms increasing, the child died without convulsions. The heart sounds before and after birth were normal; just before death the pulse fell to 30 per minute. Autopsy was made five hours after death, the body kept upon ice in the interval. On examination the left lung was compressed and pushed to one side by a large thymus, a heart-shaped organ situated slightly to the left of the median line extending from the lower border of the thyroid above, to the fourth rib below. The left innominate vein crossed the thymus and had compressed it somewhat. There was no evidence of thrombosis in the veins in this region. The heart was apparently normal, but both lungs were markedly edematous. There was no lesion of the intracranial organs, but on opening the trachea it was markedly compressed by the thymus, and its compression and its effects had evidently caused fetal death.

Brachial Birth Palsy.—Thomas (*Am. Jour. Obst.*, April, 1916) contributes a paper upon this subject reporting 11 cases with illustrations and describing his treatment. The writer has had experience with 24 palsied arms in 23 patients, and finds that there is no displacement in the shoulder-joint, and perfect recovery will be obtained from exercise alone. When a case of birth palsy is seen with the typical internal rotation of the limb and the characteristic limitation of abduction, and external rotation in a child as old as two or three, a posterior subluxation of the shoulder-joint is almost invariably present. This may be recognized by remembering the important relations at the shoulder, which are those at the upper end of the humerus to the margin of the acromion. The examining finger on making pressure finds a depression under the posterior margin of the acromion. The relation of the humerus to the anterior and posterior borders of the acromion are the important points in the diagnosis. If this dislocation can be recognized at birth, it is comparatively easy to reduce it. That this condition is the result of traumatism is shown by the bending downward and forward of the anterior portion of the acromion. This is caused by the same pressure which pushed the head of the humerus back during delivery. This the roentgen ray does not always show because the bones may be too young to give the usual shadow. Ossification in the acromion does not begin until about fifteen years of age. In many patients it is well to examine them under partial etherization, and when the diagnosis is made, to put the head of the humerus in good position and retain it by a light cast. The writer has operated upon the shoulder in 9 cases, and the elbow in 1; the incision is so planned as to give a free exposure. After this the obstructing portion of the acromion is removed. Then the effort is made to force the arm into external rotation and abduction, and to put the head of the humerus as nearly as possible into its normal anterior position. After the operation is complete, a light plaster cast is applied fixing the arm in abduction and external rotation for about six weeks. The writer has had good results from his operative treatment of these cases.

Rupture of the Pelvis.—Morgan (*Am. Jour. Obst.*, April, 1916) reports 4 cases of rupture of the symphysis. The first occurred in a woman, aged thirty-one years, eight and a half months pregnant. She had previously had a very difficult high forceps operation, terminating in the birth of a dead child. There were old lacerations and separation of the pubic bones admitting three fingers, and all of the ligaments except part of the suprapubic had been torn away. The patient was obliged to wear a belt constantly. She was easily delivered by forceps applied when the head was on the pelvic floor, and made a good recovery. She was subsequently operated upon for the prolapse of the uterus. The separation of the pubic bones remains, but the patient has discarded the belt and takes exercise freely. The second case was a primipara, aged twenty-one years, with slightly generally contracted pelvis, with long and sharp promontory. High forceps was applied when during traction the symphysis separated almost two fingers' breadth. The head was slowly delivered by the hands, having been brought upon the perineum by forceps. There was profuse bleeding, the vagina having been torn laterally, and the urethra split longitudinally. The meatus was torn. There was a cavity behind the pubes into which the bone projected. Lacerations were repaired as well as possible, and a self-retaining catheter left in the bladder. Hemorrhage had been profuse and the patient was exsanguinated. Fortunately she escaped infection, the lacerations healed, and she was discharged forty-eight days after confinement with no pain, and with normal locomotion. She still has incontinence of urine upon exertion while standing. The third patient was a multipara with generally contracted pelvis, labor was tedious, and dilatation was completed by the hand and high forceps applied. During the puerperal period the patient complained of pain and separation of the symphysis was found. On her discharge from the hospital she still complained of pain and walked badly. Case 4 was a multipara who gave a history of previous forceps delivery. It was stated that the child was stillborn, but that the operation had been an easy one. When the patient was seen six days later she had fever, rapid pulse, and profuse purulent vaginal discharge. There was great pain over both hips and sacroiliac joints, and on pressure over the symphysis there was an abdominal tumor resembling a distended bladder, but firmer, and the uterus could not be felt. On examination the cervix was badly torn and also the anterior wall of the vagina, the pubes had been ruptured and the left side stripped of its periosteum. The bones were widely separated. The patient was admitted to hospital and a tight pelvic binder applied which relieved pain. The profuse discharge continued for four or five days, but the patient finally recovered with good control of the bladder. She was obliged to wear a leather pelvic belt and could walk well without pain. She afterward had prolapse of the vaginal wall.

GYNECOLOGY

UNDER THE CHARGE OF
JOHN G. CLARK, M.D.,
PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Thorium in Pyelography.—In September of last year we referred to a paper of Burns, presenting a new substance, thorium, for use in pyelography instead of collargol. The advantages which Burns claimed for thorium were less viscosity of the solution, thus greatly facilitating its rapid elimination from the urinary system, practical absence of the irritating and toxic qualities of collargol, and much less cost (about one-third that of collargol). In a recent paper, Burns (*Bull. Johns Hopkins Hosp.*, 1916, xxvii, 157) maintains that all these claims have been justified by further experience. The method of preparing the solution is of importance, and is the same as that given in the previous paper, and quoted in full in the above-mentioned abstract. Burns reports that the thorium solution has now been used in 125 cases without a single untoward result. It has been used in varying amounts up to 600 c.c. in the upper urinary tract and up to over 900 c.c. in the bladder. There have never been any evidences of urinary disturbance following its use, and subsequent cystoscopic examinations have shown no evidence of inflammation of the vesical mucosa. In cases where operation within a few hours or days has permitted of examining the bladder, ureters, and kidney pelves after the use of thorium no evidence of irritative action has ever been found. Extensive animal experiments have shown no signs of peritonitis after injection of large amounts of the fluid into the peritoneal cavity; in a few instances, however, death of the animal has occurred after the injection of large doses intraperitoneally or intravenously, though even larger doses in other instances have produced no ill effects. The high degree of fluidity of the solution is shown by the fact that roentgen-ray plates made a few minutes after the injection has been discontinued give no suggestion of a shadow, thus proving that the thorium has been completely eliminated from the urinary tract. The solution is exceedingly opaque to the roentgen ray and gives a shadow of great clearness and brilliancy. Its stability is not in the least affected by sterilization either by steam under pressure or by boiling. If the experience of Burns shall be confirmed by others it would appear that in the thorium solution devised by him we have an ideal agent for pyelographic work which will remove many of the very real drawbacks that have heretofore accompanied this valuable diagnostic procedure.

Unilateral Hematuria Associated with Microscopic Calculi.—The etiology of unilateral hematuria in the absence of demonstrable calculus or tumor formation is often an exceedingly puzzling question. Of late, chronic inflammation has been considered by several authors to be the underlying factor in this condition; in this connection a case recently reported by Paine (*Surg., Gynec. and Obst.*, 1916, xxiii, 76) is of much interest, as it throws some additional light on this exceedingly obscure pathological condition. Paine's patient had been suffering from occasional blood in the urine for seven years, this having been practically continuous for the last three years. There was never any pain, colic, or fever, but there had been some loss of weight. There was no mass or tenderness in either kidney region, and roentgen ray was negative for stone. The microscope revealed an abundance of blood in the urine, but no pus or casts. Cystoscopic examination showed a normal bladder, with bloody urine spurting from the right ureter and normal urine from the left side. Urines collected by ureteral catheterization showed the same distinction. Functional tests showed normal elimination from the left side, but marked reduction on the right. A few colon bacilli were found in the urine from the right kidney; that from the left was sterile. At operation the right kidney appeared normal in size, and no stone or tumor could be demonstrated. Upon bisection the kidney tissue showed nothing definite, except that every papilla was intensely congested, the tip of each presenting a cherry-red appearance which coincided macroscopically with the classical description of an angioma. It did not seem reasonable to suppose that bisection with suture could relieve this condition, and in view of the normal functional test of the opposite kidney, nephrectomy was considered justifiable, and was performed. On examining the extirpated kidney the pyramids all appeared markedly congested, this congestion taking the form of streaks running in the long axes of the pyramids, and in several instances leading to areas of reddish-brown congestion which surrounded their apices. Microscopically there was no increase in the intertubular connective tissue of the cortex and no sclerosis of the vessels. In the region of the papillæ, however, there was a distinct connective-tissue increase, this being not uniform in its distribution, but for the most part limited to the immediate neighborhood of numerous calculi of microscopic size found throughout the papillæ. In these localized areas of connective-tissue overgrowth the small veins and capillaries were hugely dilated into venous sinuses. All the papillæ showed also dilated capillaries on the surface, many of which were ruptured, with free blood escaping. While the author admits that the origin of these varicosities, from which the hemorrhage evidently came, is not clear, he considers it probable that the numerous though small calculi, aided by the connective tissue they had originated, succeeded in causing an obstruction to the venous return and a subsequent dilatation of the capillaries with resulting varicosities. So far as deductions can be drawn from a single case, therefore, the theory that chronic inflammation may be the underlying cause of so-called essential unilateral renal hemorrhage would appear to be strengthened by the facts here presented.

Primary Urethral Carcinoma Treated by Radium.—An extreme interesting case of this very rare condition has recently been the subject of a brief report by Shoemaker (*Surg., Gynec. and Obst.*, 1916, xxii, 730). The patient was a negress, aged fifty years. For five months previous to coming under observation she had experienced gradually increasing difficulty in micturition, with extreme bladder distention the last week, and complete retention on admission to the hospital. The urethra could be felt through the vagina as a hard, fixed ridge the size of a lead-pencil, extending from the meatus nearly to the base of the bladder. The external meatus was retracted, its edges hard, irregular, and nodular. There was no involvement of the cervix, uterus, or vagina. With some difficulty a small ureteral catheter was introduced through the urethra and left in place. After some days a larger catheter was passed, but the retention persisted. Surgery was considered inadvisable, as it would have been necessary to remove the entire urethra up to the neck of the bladder, with resulting incontinence. Recourse was therefore had to radium treatments, nine applications of 20 mg. of radium element, of three hours each, being made in the course of about three weeks. The first few drops of urine were passed spontaneously about ten days after the first treatment, the quantity then gradually increasing, until soon after the last treatment the bladder could be completely emptied in a normal manner. The urethra still retained its pencil-like feel, however, and a small piece of tissue removed at the edge of the meatus showed microscopically a squamous-cell carcinoma. The inguinal lymphatics were not palpably enlarged, but their removal was advised, whereupon the patient disappeared, considering herself well. It is evident, therefore, that a definite cure cannot be claimed for the radium treatment in this case; nevertheless, such might have eventually been attained had the patient remained under observation, and, at any rate, it seems probable that a greater amount of amelioration was obtained than would have been possible by any other means.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,
PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

JOHN F. ANDERSON, M.D.,
FORMERLY DIRECTOR OF THE HYGIENIC LABORATORY, PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Effects of Refrigeration upon Larvæ of Trichinella Spiralis.—Until two years ago, it had been generally accepted as an established fact that the larvæ of Trichinella spiralis are very resistant to cold and that they survive exposure to temperatures much below the freezing point of water. Ransom (*Science*, New York, 1914, xxxix, 181) in a brief article showed that the former ideas concerning the resistance of trichinæ to cold were erroneous, and that as a matter of fact low temperatures have a very pronounced effect upon the vitality of these parasites. Ransom, in a recent article (*Jour. Agricult. Research*, January 31, 1916) gives the results of experiments on the effects of low temperatures upon the trichinous larvæ. In the practical application of refrigeration as a means of destroying the vitality of trichinæ, meat should be refrigerated at a temperature not higher than 5° F. for not less than twenty days, a period which allows a probable margin of safety of nearly ten days. The employment of higher temperatures of refrigeration as a means of destroying the vitality of trichinæ is not justified in the light of our present knowledge because of the uncertainty of the effects of such temperatures. Whether temperatures higher than 5° F. may be safely employed by lengthening the period of refrigeration remains to be determined. It is at once evident that refrigeration is a better safeguard than microscopic examination. The combination of refrigeration and thorough cooking would protect man against trichinosis.

The Prophylaxis of Tetanus.—A valuable summary of the literature on the prophylaxis of tetanus has been written by A. T. MacConkey (*Brit. Med. Jour.*, December 11, 1915). Regarding the value of prophylactic injections of antitetanic serum, the author says that the experience of the British Army has shown that the proceeding has a well-established value, for in the last six months there have been only 36 cases of the disease among those who received a preventive dose of serum within twenty-four hours after being wounded. The accompanying table shows the results which other investigators have obtained:

Investigator.	No. of wounded.	Cases of tetanus.	No. injected.	Cases among them.
Bazy . .	10,896	129	100	1
Hartmann .	3,373	43	Number not given	No cases reported.
Gasch . .	700	1	70	0
Hufnagel .	2,193	27	1,195	0
Goldscheider	1,427	4	500	4[1]
Madelung .	15,134	101	Number not given	No cases reported.
Heile . .	...	...	4	0

The author's conclusions that although too great reliance should not be placed upon the figures quoted, yet from this experimental evidence it may be gathered that the army medical officers have found tetanus antitoxin of great value when used prophylactically, thus confirming by the severe test of active service the value as estimated before the war. The author next discusses the number of U. S. A. units of antitoxin which should be given as a prophylactic dose. In considering this matter, it becomes necessary to specify the kind of unit referred to as 1 German unit—40 U. S. A. units, while various investigators—Behring, Rosenau and Anderson and MacConkey have found the number of U. S. A. units in samples of French serum to vary, the general conclusion being, however, that the usual prophylactic dose of 10 c.c. of Pasteur Institute serum equals some 600 U. S. A. units. The doses recommended by fifteen different writers are cited, and the conclusion is drawn that from 500 to 1000 U. S. A. units of tetanus antitoxin is a sufficiently large prophylactic dose for the great majority of injuries, provided it is given early. Some cases are described, however, in which the injection of from 1500 to 4000 U. S. A. units seems to have had only a comparatively limited effect, if any, in preventing the onset of an attack. In some, the interval between the injection and the onset of the disease was too short to allow of the development of the full effect of the antitoxin. "The most remarkable of these," says the author, "is that recorded by von Behring, in which one of his assistants, who had twice before been injected with tetanus, was the third time infected by a flask of tetanus bouillon breaking in his hand and pieces of glass penetrating deep into his palm. Careful antiseptic treatment was immediately given and a plentiful amount of antitoxin injected. On the fifth day there was obvious tetanus which, in spite of further injections of serum, increased in severity, so that on the seventh day the chief nerve trunks in the right axilla were exposed and as much as possible of von Behring's strongest solution was injected, with the result that the case slowly recovered." As to the duration of the passive immunity conferred by a dose of antitoxin, the author says this is a question which has been investigated, but is still unsettled. He cites an experiment by Meyer and Ransom which showed that the passive immunity conferred on the leg of a dog by an amount of antitoxin sufficient to neutralize all the toxin injected began to pass off in a week. The experiments of Ruediger are quoted as showing that the subcutaneous injection of 1500 U. S. A. units of antitetanic horse serum into a horse confers a passive immunity lasting from six to eight weeks and that 250 U. S. A. units of similar tetanus antitoxin will protect guinea-pigs for four weeks, *vs.* a dose of toxin fatal to the control animals. Calculating from these figures, MacConkey found that according to body weight only a man weighing 70 kilos would require 3500 U. S. A. units of antitoxin to protect him for a month against a fatal dose of tetanus toxin. Leven, in his work, states if 10, 20, or 40 c.c. of heterologous serum be injected into a rabbit practically all has disappeared at the end of about six days, and that if it is wished to keep the antibody concentration at a certain height for some time, it is better to give a series of relatively small doses and not one very large one. The conflicting results of several cases, in one of which 12,000 units protected for only thirteen days, while in another 1500 units conferred immunity for over three weeks, and the experience of the British Army that small dose—500 U. S. A. units—is many times effective, lead the author to agree with Leven in his conclusion that if necessary to give a large amount of antitoxin it is better to give a series of small doses rather than one large one. Other cases which are puzzling are those in which tetanus develops late, and these are next discussed by the writer. He mentions various causes found by investigators to be responsible for late development of tetanus infection in hospitals from one patient to another, infection from felt which was used in two cases as a packing for a plaster corset, infection from an East Indian fiber used for dressing wounds, activation of tetanus spores which had been introduced in vaccine viruses by the late injection of Staphylococcus or quinin. The author also cites the work of several other workers who report cases of tetanus following some slight operation or trauma affecting a wounded soldier who had been treated with a prophylactic dose of serum and had apparently long recovered from his wound. A case was described in which the infection was possibly due to too early and prolonged activity after the healing of the wound. Regarding operating in cases of tetanus, the author says the experiences during the war have not changed opinion in respect to that, since it has been shown by Bolton and Fisch (1902) that toxin makes its appearance in the blood of a horse several days before the symptoms of the disease appear, and that it increases until about two days before the symptoms are noticed, when it suddenly diminishes. The author reports a number of cases which confirm these facts and show that operating is ordinarily of no effect because the toxin is already present in the blood. When an operation is proposed in wounded who have been infected with tetanus, MacConkey emphasizes the fact that it is imperative to keep in mind that there may be toxin circulating in the body and thererfore that a large prophylactic injection is necessary which should be given in such a way as to ensure that there is no free toxin in the blood at the time of the operation and for some time after. The injection must be given either intramuscularly, in which case the operation should not take place for some hours, or intravenously. In the latter case the operation can be performed immediately, but it involves the possibility of anaphylactic trouble. The conclusions which the author draws are: (1) That from 500 to 1000 U. S. A. units of tetanus antitoxin is a sufficient prophylactic dose for the majority of cases, but that it is advisable in severe wounds to repeat the dose once or twice at intervals of a week. (2) The occasional cases in which antitoxin appears to have little preventive effect should be recorded in minute details. (3) Those cases of tetanus which develop some weeks after the reciept of an injury may be due to the reactivation of a quiescent focus by too early or too energetic active or passive movement.

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[1] Such cases should probably not be included, as there were other complications.

Industrial Poisoning with Analin.—Luce and Hamilton (*Jour. Am. Med. Assn.*, May 6, 1916, lxvi, 1441) point out that industrial poisoning from analin and substances closely allied to it is well known in Germany and in Great Britian. It is just beginning to be known in the United States, where it has already been the cause of many cases of poisoning among men engaged in the manufacture of rubber goods, in reclaiming rubber from scrap, in making analin from benzene, and in using certain washes for press rollers. It also occurs in the dye industry. Analin causes the formation of methemoglobin and poisoning may take place through the skin or the lungs. Exposure to the fumes need not be excessive nor long continued to bring about serious symptoms in the susceptible. Young men are more susceptible than the old or middle-aged, blonds than dark-haired men, heavy drinkers than the temperate. Hot, humid weather, heated rooms, and poor ventilation are important factors in the production of acute analin poisoning. Early recognition of analin poisoning is of prime importance, so that the sufferer may be withdrawn from the danger of further exposure. Men working constantly in analin seem to acquire a certain amount of tolerance to it, but chronic poisoning may result apparently from cumulative effect. After symptoms of poisoning have once manifested themselves, the individual is usually hypersensitive to the fumes.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
JOHN McCRAE, M.D., M.R.C.P.,
LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL;
SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT,
BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL
VICTORIA HOSPITAL, MONTREAL,

AND

OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH,
PITTSBURGH, PA.

Studies on Crown Gall of Plants and its Relation to Human Cancer.—The author of this work, Erwin Smith (*Jour. Cancer Res.*, 1916, i, 231), has done very extensive work upon the bacteriology of plants. His particular interest has been to demonstrate the importance of certain bacterial infections to plant disease. In his investigations he has shown that many of the different blights, rots and wilts of plants are the result of bacterial invasion. Besides this he has also shown that specific parasites are capable of stimulating overgrowth of plant tissues causing hypertrophic masses to develop. Not only has he studied the pathological processes in spontaneous disease of plants but he has also reproduced them by experimental means. Two of the striking types of simple overgrowth have now become well known. These are found in the root nodules of the leguminosæ and the club-foot enlargements of the crucifers. In these pathological processes the individual cells of the tissues are stimulated to overgrowth and multiplication by the presence of bacteria lying in the cell interstices. The author believes that crown gall is a disease of plants which in its development and growth bears striking similarity to human cancer. Crown gall is a growth very common to a great variety of plants the world over. This tumorous growth shows cellular characters and types of nuclear division comparable to that of animal tumors. Metastases are produced by the extension of the growth along the vascular channels and by the migration of the causative agent to new areas. He believes that these tumors are to be differentiated from reactionary (inflammatory) processes in which the local cells respond for the purpose of healing. The effect of these tumor masses upon the remaining plant structure resembles in part the cachexia and anemia of animals. Smith has found that these plant tumors are the result of the presence of an intracellular infection which may be isolated and used to inoculate unaffected plants. Success has been obtained in these inoculation experiments and new tumors have arisen at the points of inoculation. These experimental tumors are similar to those of spontaneous origin. The organism causing this plant tumor is a schizomycete named B. tumefaciens. As this microörganism is killed at 37° C. its invasive properties of higher animals cannot be assumed. Attempts were made to reproduce in cold-blood animals tumor growths by the inoculation of this bacterium but no satisfactory results were obtained. The author believes that although no parasite has been demonstrated for animal tumors the analogy between the new growth in plants and animals suggests that the causative agents are similar.

Fetal Erythroblastosis.—Varying types and grades of edema are not uncommonly observed in the newborn. One type, congenital general edema, although not rare in its occurrence, has not been extensively commented upon. This form of congenital edema is usually seen in premature fetuses in which excessive fluid is found in the tissues of body cavities. This edema also involves the placenta and cord. The liver and spleen are enlarged and show numerous islands of myeloid cells and immature red cells and leukocytes. Various causes have been assigned for this congenital disease. Disturbances in the portal circulation, anomalies of heart, maternal nephritis and metabolic disturbance of the fetus have all been suggested as the active cause leading to this systemic disease. WOOLLEY (*Jour. Lab. and Clin. Med.*, 1916, i, 347) observed these characteristics in a case of congenital edema. The fetus was one of twins. He believed that the anasarca was the expression of the anemia resulting from disturbed production or increased destruction of erythrocytes. The pigmentation of the organs suggests an increased blood destruction. The low oxygen carriage of the impoverished blood diminishes metabolism and with it it is thought an accumulation of acids. The anasarca is, therefore, the expression of a severe grade of anemia. The author offers no suggestion for the origin of the anemia.

Experimental Arthritis in the Rabbit.—There has been much discussion upon the significance of various bacteria isolated from cases of arthritis and although experimental joint lesions have been obtained in animals little agreement is to be found in the interpretation of these results. The joint affections receiving greatest attention have been those associated with rheumatic fever. In this disease one or other of the types of Streptococcus viridans has been isolated. In carrying on inoculation experiments with these microörganisms joint lesions may be produced without, however, any degree of constancy which may be controlled. There are factors which appear to have a bearing upon the specific tissue infection which in part is related to the size of the inoculated dose, the virulence of the microörganism and the susceptibility of different tissues. That the latter condition plays an important part has often been suggested but very little experimental evidence has appeared to indicate the truth of the statement. FABER (*Jour. Exper. Med.*, 1915, xxii, 615) has brought forward a very interesting report upon a series of experiments in which the importance of a previous sensitization of tissues, particularly joints, rendering them more susceptible to an active infection and inflammation was shown. In these experiments rabbits were sensitized either by inoculating them intravenously with one or more doses, or by injecting dead cultures of streptococci into a joint. After a varying period of time an intravenous inoculation of the same living microörganisms was given. By the latter method a condition of sensitization was obtained so that it was possible to cause arthritis in rabbits by intravenous inoculation. The reaction appeared specific in that the joint response could be obtained only by means of the same type of organism used in sensitizing. When animals are treated by the intravenous route alone, localization was best attained after the giving of several doses. This feature the author believes is similar to the recurrences to which the rheumatic patient is liable. This work by Faber is very suggestive and particularly important in drawing our attention to some specific qualities which may be contained within tissues and which are of importance in making those areas more vulnerable.

Heteroplastic Bone and Bone-marrow Formation Associated with Tuberculosis in the Adrenal.—Aberrant islands of bone are not uncommonly met with in a great variety of organs and tissues. The frequency of meeting with heteroplastic bone is in direct proportion to the opportunity of microscopically analyzing tissues which are too frequently superficially diagnosed by the naked eye. In the fibrosed tonsils of elderly individuals bone and cartilage are commonly seen in the thickened capsule. Similarly, bony islands are frequent in the calcified media of the peripheral arteries. Osteoid and true osseous tissue are also encountered in the ovary, lung, and lymph glands. In the latter tissues the bony deposit is closely associated with the calcareous masses arising in advanced tuberculosis. WOOLLEY (*Jour. Lab. and Clin. Med.*, 1916, i, 502) observed heteroplastic bone in the adrenal with chronic tuberculosis. The specimen was obtained from a man, aged forty-two years, suffering from widespread tuberculosis which had also attacked the adrenal. The old lesion was situated in the medulla while more recent tubercles were present in the cortex. The bony mass in the medulla was well developed and contained a myeloid tissue within which there were several miliary tubercles. The author believed that the bone had developed in association with a chronic tuberculous focus about which a secondary metaplasia of the connective tissue was stimulated by the infectious necrosis. The presence of bone in the adrenal is quite unusual but the manner of its development is probably similar to that observed in other tuberculous areas.

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ORIGINAL ARTICLES

THE DIAGNOSIS AND GENERAL TREATMENT OF SYPHILIS.

By John A. Fordyce, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

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It cannot be emphasized too frequently nor too emphatically that the fate of the syphilitic individual depends largely upon the early diagnosis of his infection and the intensity with which his treatment is carried out in the first six months. It is in the accomplishment of this purpose that the modern aids to diagnosis have rendered such invaluable service. Unfortunately, this is not universally recognized, for clinicians are still met with who decry these modern precision methods, claiming that the trained observer can recognize with his eye and sense of touch all that can be revealed by laboratory procedures. The fallacy of this claim is demonstrated from time to time by patients who come with the following history: Fifteen to twenty years ago they consulted the best-known syphilographer at that time, who made a diagnosis of chancroid, telling the patient that his future, as far as the present infection was concerned, was secure and that he had nothing to fear. Reassured by such information no treatment was taken, and years after these patients consult for involvement of the central nervous system, an interstitial glossitis, an aortitis, or other late manifestation of the disease. It is now well known that the soft sore frequently harbors the parasite of syphilis, and owing to the longer incubation period of the latter, does not develop its characteristic features until after the expiration of two or three weeks, or they may be entirely absent. It seems superfluous, therefore, to insist that the secretion of all venereal sores be searched for the Treponema pallidum. Failing to find it, one should not give a favorable prognosis until repeated examinations have been made, including the Wassermann reaction. With proper training the dark-field illumination is simple of application and the spirochete of syphilis readily differentiated from other types. Microscopic corroboration of a suggestive sore is absolutely essential in many cases, owing to the protean appearance chancres may assume. While, to the skilled eye and finger, a Hunterian chancre with indurated edges needs no confirmation, the pathognomonic features may be lacking altogether, or a papule or herpetic lesion may represent the only local reaction called forth by the treponema. In urethral sores and suspicious extragenital lesions the correct and early diagnosis is of great importance, and their nature finds a ready means of differentiation in the dark field. The value of the latter is further appreciated in developing chancres before the clinical characteristics suggestive of the infection appear. Recently, I had the opportunity to examine an initial lesion which had made its appearance only on that day. It was situated on the left side of the foreskin, was about the size of a pinhead, capped by a tiny crust. The patient had been exposed three weeks before. There was no lymph-node enlargement and the Wassermann reaction was negative. The advantage of early treatment in such cases and consequently the more favorable prognosis are too obvious for discussion. Success in demonstrating the organism depends largely on the care taken in obtaining serum for examination. This should be secured from the depths of the lesion. Antiseptic washes, ointments, or other applications frequently interfere with the demonstration, and in cases of doubt the examination should be repeated on successive days, the lesion being kept clean meanwhile with saline solution.

The time of the appearance of the Wassermann reaction cannot be estimated with mathematical exactness, as it is dependent upon the rapidity with which the organisms gain the general circulation and the reaction provoked by them. This we know varies in different individuals. In some cases the reaction is positive in the fourth or fifth week after exposure; in others not until the seventh or eighth week. A negative reaction does not necessarily mean that generalization of the spirochetes has not taken place. Uhlenhuth and Mulzer[1] obtained positive results in animal inoculations with the blood of primary syphilitics in whom the Wassermann reaction was still negative. With the development of the rash it is usually definitely established. I have in a very long series of untreated cases found only one with a fresh maculopapular eruption in which the Wassermann was only weakly positive. If treatment is carried out on a definite and intensive plan in the primary stage a negative reaction will remain continuously negative, or in the event of its being already positive it shows itself susceptible of reversion more readily than when the infection is of several years' duration. Too much stress cannot be laid on the fact that the amount of treatment is individual; this must be kept in view in every case under consideration. There are patients treated under the old régime with mercury by mouth, inunctions or injections, or these methods combined, who now have a negative blood reaction, exhibit no symptoms referable to the nervous or circulatory system, and are negative after a provocative injection of salvarsan. Others treated five years ago with a minimum amount of salvarsan (*i. e.*, one or two injections) and mercury may likewise be considered cured according to our present-day criteria. On the other hand, there are a certain number of patients in whom multiple courses of salvarsan and mercury are necessary to bring about and maintain negative findings. In some cases we will even fail to convert a positive into a negative reaction without endangering the health of the patient. A resistant serum cannot always be accounted for on a clinical basis, for often, as far as we are able to ascertain, nothing can be demonstrated to explain its persistence. In by far the vast majority, however, involvement of the cardiovascular or nervous system will furnish an explanation.

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[1] Berl. klin. Wchnschr., 1913, p. 769.

The interpretation of the Wassermann reaction is as important as that of the clinical phenomena of the disease, but the burden of proof should not rest with its presence or absence alone. In ocular syphilis, disease of the vascular apparatus, obscure visceral or nervous involvement and in latent syphilis of hereditary origin positive manifestations may be present and the Wassermann reaction negative. To make some of these points clear the following cases are quoted:

Case I.—Man, with active secondary skin and throat lesions at end of October, 1914. On October 31, November 8 and 20, and December 13 respectively, 0.6 gm. salvarsan. January 8, 1915, perivasculitis. Wassermann said to have been negative. Under rubbings and calomel, eye lesions cleared. Discontinuance of treatment was followed by relapse from a new focus. March 31: Spinal fluid, ——; serum, ——. Under injections of a soluble salt and potassium iodide the eyesight again improved. Treatment interrupted in September. Wassermann, December 29, 1915, March 16, 1916, + + + +.

Case II.—Man, aged fifty-seven years, with cerebral endarteritis and capillary fibrosis at the maculæ. Infection over thirty years ago. Recurring ulcerative skin lesions; scaling eruption palms; mental depression, vertigo, loss of memory; inability to concentrate on work;

failure of sexual power. He recalls severe headaches, leg pains, and mental excitability in secondary period twenty-nine years ago. Eye reflexes, knee-jerks, and ankle-jerks present without noticeable abnormality. Treatment during many years with mercury and potassium iodide. Repeated negative Wassermann reactions during 1911 and 1912. In 1913, after treatment with potassium iodide and mercury, Wassermann became + + + +, and after further treatment ——. Spinal fluid March 31, 1915: cells, 0; globulin, + +; Wassermann, ——; gold test, ——; blood Wassermann, + + + +. Treatment continued during 1915 was followed by improvement in all respects. Vertigo and depression disappeared; capacity for work increased. He was less excitable and memory and sexual power returned. Evidence of vascular disease in eye also disappeared.

The noteworthy features in this case are the long persistence of a negative Wassermann reaction, with scaling palms analogous to leukoplakia, the obscure character of the nervous symptoms, evidence of vascular disease in eyes, result of fluid examination pointing to cerebral endarteritis, Wassermann reaction becoming positive after treatment by iodides and mercury, and relief of all symptoms by persistent treatment.

Case III.—Girl, aged twenty-one years; hereditary syphilis. Scars of an old interstitial keratitis. For five years had suffered from migraine type of headache. Serum ——; spinal fluid ——. After three injections of salvarsan serum became strongly positive.

Case IV.—Man, aged forty-nine years; chancre when sixteen years old, followed by secondaries. For three years internal treatment; no relapses. In the summer of 1915 he complained of increasing fatigue and soreness over the right apex. Repeated examinations for tubercle bacilli negative. Von Pirquet, +; Wassermann,——. From roentgen-ray and physical examination, diagnosis of syphilis of the bronchial glands was made. Wassermann, January 7, 1916, ——; January 11, 1916,——; mixed treatment for one week evoked a + + + + reaction.

The above abstracts show that not rarely it requires not a single but several injections of salvarsan or the prolonged use of mercury and potassium iodide before a provocative reaction is obtained.

The Wassermann test is of great value in the recognition of syphilis as a causative factor in conditions of obscure etiology in children. Also in anticipating future development, as in many cases of congenital syphilis no sign or symptom is present excepting a positive blood reaction. The children are normal mentally and physically, and excepting the positive serum and a history of syphilis in the father there is nothing suggestive of a luetic taint.

The tendency of the present day is to deny categorically the paternal origin of syphilis, admitting only the possibility of transmission from the maternal side. While this would simplify the problem it offers no solution for the cases in which the mothers remain symptom-free and Wassermann-negative; some patients observed after thirty years who have had one or more children clinically and serologically syphilitic. Do such women have a modified form which disappears spontaneously or do they escape the infection altogether?

The only criterion of cure in a man contemplating matrimony is a negative Wassermann which has persisted for at least a year after intensive treatment and which remains negative after a provocative salvarsan. The element of time while of importance in modifying the infection is of vastly less value than the revelation of the serological test. In a family seen by me a short time ago the father was infected in 1901, for which he had inunctions and potassium iodide each year for six years. He was married in 1907. The first child was born in 1908, was well nourished and healthy until August, 1915, when he developed partial deafness of the right ear. His spinal fluid showed: cells, 20; globulin, + +; Wassermann, ——; serum, + + +. The second child was born in 1913, is splendidly developed in every way, and has never shown any symptoms but has a + + + + Wassermann. The mother's reaction is negative; she has never given any evidence of the infection, has had no miscarriages and no treatment. The father's reaction is + + + +.

The diagnostic import of the spinal-fluid examination grows more and more apparent with time. The cell count, Wassermann reaction, globulin and colloidal gold tests enable us not only to determine the activity of a syphilitic process in the brain or cord but serve to distinguish the various pathological types of syphilis affecting the cerebrospinal system and in many cases to differentiate between these and non-luetic affections. A case in point is the simulation of the multiple neuritis of diabetes by the tabetic syndrome.

A patient, aged thirty-seven years, was referred to me with the diagnosis of tabes. He had had a chancre twelve years before, followed by secondaries and treatment for three years. For four weeks he had had pain and numbness in his fingers and feet, with an insecure feeling in the soles of his feet, difficulty in walking and unsteadiness. For six or seven years he had had periodic attacks of gastric distress, with dizziness and extensive areas of hyperesthesia; sexual paresis had been present for one year; eyes were normal; patella and Achilles reflexes absent. Laboratory examination showed: blood Wassermann, ——; spinal fluid; cells, 8; globulin, ——; Wassermann, ——. His urine contained a large amount of sugar. Diagnosis: diabetic polyneuritis.

Another case was sent with the diagnosis of taboparesis. The patient gave a history of syphilis twenty-five years previously, with repeated courses of treatment. His pupils were irregular and fixed to light, knee-jerks absent and lightning pains in the lower extremities. It was claimed that he had shown evidence of mental deterioration as manifested by irascibility, loss of memory, etc. The patient had been an alcoholic for over thirty years, having taken six to eight drinks daily, with occasional intermissions. His blood and fluid examinations were absolutely negative. In this case a correct diagnosis might have been made by a skilled diagnostician, but to the average practitioner the picture presented was that of tabes or taboparesis. From the laboratory stand-point there are two possible conclusions: either the spinal-fluid findings were rendered negative by the treatment received or the entire syndrome was due to alcoholism and the question of syphilis as an etiological factor left in doubt. The latter supposition is the more probable, experience having shown that in paresis, negative findings throughout are not brought about by the amount of treatment the patient has had.

With faulty diagnoses like the above on the negative side of syphilis, those on the positive side merit citation, for not infrequently patients with obscure pains, febrile attacks, gastric and rectal crises, irritability, failure of memory, etc., give a history of having long been treated for neuresthenia, rheumatism, neuritis, and various other indefinite conditions. Such patients sometimes admit having had a specific infection with indifferent treatment; others disclaim all such knowledge.

One of my clinic patients, a young woman, aged twenty-four years, had within the past two years about twenty attacks of gastric crises. She was usually removed to a hospital, and on two occasions was operated upon, once for appendicitis and again for gall-stones. She has been married five years and has had several miscarriages. The only objective manifestation of tabes was slightly sluggish pupils. Her serum was strongly positive, her spinal fluid showed 45 cells, + + globulin, Wassermann + + + + to 0.6; colloidal gold, luetic curve.

Rectal crises are less commonly seen and their nature often fails of recognition. A patient under my care was treated nineteen years ago for primary and secondary syphilis. For the past two years he had had attacks of severe pain in the rectum, for which an operation had been advised. His pupils were unequal and sluggish to light, knee-jerks normal, station good, bladder slow, sexual power weak. Blood, + + + +; spinal fluid; cells, 150; globulin, + +; Wassermann, + + + + to 0.4; colloidal gold, luetic curve. His pains were markedly aggravated by the first few intraspinal treatments.

The so-called lightning pains in tabetics are often treated symptomatically or disregarded entirely.

A patient, aged thirty-four years, infected ten years ago, had suffered from pains in his legs for seven years. His spinal fluid showed: cells, 42; globulin, + +; Wassermann, + + + + to 0.2; colloidal gold test, luetic curve; serum + + + +.

Another patient, aged thirty-nine years, infected seven years ago, complained chiefly of stabbing pains in various parts of the body which began four years ago in the lower extremities. His pupils were irregular and sluggish to light, his knee-jerks weak, ankle-jerks absent. Spinal fluid: cells, 8; globulin, + +; Wassermann, + + + + to 0.2; colloidal gold test, luetic curve; serum + + + +.

The premonitory symptoms of developing paresis are also frequently overlooked. This is illustrated by the following case:

Man, aged forty-two years, infection in 1905, for which he was treated for seven years with mercury internally and by injection. He had had no symptoms since 1912. In June, 1915, he had a convulsion, unconsciousness lasting one-half hour. The attack was attributed to colitis and intestinal absorption and treatment directed against this until December, 1915, when he had a second convulsion. His spinal fluid showed: cells, 45; globulin, + + +; Wassermann, + + + + to 0.1; colloidal gold test, paretic curve; serum, + + + +.

In the light of more recent investigations an analysis of the spinal fluid is not complete unless the gold sol test is performed in addition to the Wassermann reaction and cytological and chemical examination. The theory of this reaction is based upon the observation made by Zsigmondy in his original work on metallic colloidal solutions in 1901, that solutions of electrolytes precipitate colloidal gold; that in the absence of an electrolyte, proteins will also cause such a precipitation, while in the presence of an electrolyte they inhibit precipitation. These principles were applied by Lange[2] in 1912 to the examination of the spinal fluid. He found that by a modification of the Zsigmondy technic, normal and pathological fluids could be differentiated from each other as well as syphilitic from other affections of the central nervous system. While the test has been employed by a number of workers during the past few years in the diagnosis of syphilis, it has not had the general application it deserves owing to the difficulty of making the solution. This phase happily is now in large measure overcome by the admirable work of Dr. Miller[3] and his associates. Through their investigations every detail in connection with the technic of its preparation has been so carefully developed that the standardization of the reagent is now possible, and consequently more uniform results in the reaction.

Just how the reaction occurs and the nature of the protein or proteins involved is not known. Views advanced are that it is due to the presence of abnormal albumin or possibly the presence of an excessive amount of the normal. It was originally found that the colloidal gold was a qualitative determination which, according to dilution, gave different reactions. Lange, therefore, sought the explanation in a different qualitative mixture of proteins while Zalozieki interpreted it as an immunity reaction, and Jaeger and Goldstein as a physical phenomenon of an electrical nature. Miller, Brush, Hammers, and Felton have shown that the substance is dialyzable. The amount of albumin normally present in the spinal fluid gives no reaction and a change in reaction is therefore indicative of some abnormality as to quantity or quality.

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[2] Ztschr. f. Chemotherapie, Orig., i, 1912, p. 44.

[3] Bull. Johns Hopkins Hosp., xxvi, 1915, p. 391.

The test itself, very easily and quickly made, consists of a series of color changes which occur so characteristically and constantly that they may be said to be specific. It is performed with ten dilutions of spinal fluid in geometrical progression from 1 to 10 to 1 to 5120. The color change depends on the amount of colloidal gold precipitated and varies from the negative salmon red through red blue, lilac or blue, blue gray or gray, and colorless. These changes may be plotted in curves or are arbitrarily expressed from zero to five. A negative colloidal gold would show no change and would therefore be expressed as 0000000000. In tabes and cerebrospinal syphilis the reaction occurs in the lower dilutions with the intensity of the change in the third and fourth or fourth and fifth tubes. The term "luetic zone" or "luetic curve" is used to describe this reaction. The reading would be as follows: 1133200000 or 1223320000. In meningitis of non-syphilitic origin the maximum change occurs beyond the syphilitic zone—that is, in the higher dilutions—while in paresis precipitation of the colloidal gold occurs regularly in the first four to eight tubes with decolorization or a turbidity, and the reading represented as 5555431000 or as many fives as there are decolorized tubes. To this zonal change Miller and Levy applied the term "paretic curve." A properly standardized—that is, a neutral solution of colloidal gold—shows either no change at all with a normal spinal fluid or produces a slight variation with a bluish nuance in the first four or five tubes which is negligible. Some cases may even give a change to a frank red blue in the first four tubes, so that the reading would be 1111000000, but with all the other laboratory findings negative it has been shown this had no diagnostic import.

It may be said that, as a rule, there is a parallelism between the other positive findings in the fluid and a positive gold reaction. The significance of any one of the individual abnormalities must be appreciated before a proper interpretation can be placed upon the laboratory findings. We know that a lymphocytosis alone is not pathognomonic of syphilis as a mild grade is met with in other affections of the central nervous system and that the cell count cannot be relied upon to differentiate between tabes, cerebrospinal syphilis, and general paresis, as an equally high pleocytosis may be met with in any of these conditions. So too the presence of globulin alone indicates organic disease of the brain or cord, but does not separate syphilitic from non-syphilitic disease. More positive information is derived from the complement-fixation test, as a positive Wassermann occurs only in lues. However, this test by itself does not supply a differential diagnosis as fixation to 0.2 c.c. or lower is met with not only in paresis but in some cases of progressive tabes and cerebrospinal syphilis. On the other hand, with a distinctly syphilitic process, as in cerebral endarteritis, abortive or stationary forms of tabes, and some types of cerebrospinal syphilis, the Wassermann may be completely negative. In the last-named cases a supplementary gold test is of value in demonstrating the luetic nature of the condition. Its greatest value and by far most prominent rôle, however, is in distinguishing between paresis and the conditions which simulate it as well as its prognostic significance in tabetics who show no mental impairment but give a paretic curve. Since the application of the gold sol test in my laboratory a number of patients in whom no cerebral involvement was suspected have given the curve characteristic of paresis. The following cases may be cited as illustrations:

Mr. X., aged thirty-nine years; infection thirteen years ago; secondaries denied. Mercury internally for one and a half years. In 1914 he developed pain in the legs, arms, and neck. When seen by me in March, 1915, his pupils were fixed to light and accommodation; knee-jerks and Achilles-jerks were absent: Romberg was present; slight bladder incontinence; sexual power weak. Spinal fluid examination: cells, 75; globulin, + +; Wassermann, + + + + to 0.4; colloidal gold, decolorization in first five tubes (5555543200). His family had observed no mental trouble, although they thought he had been more irritable and less dependable in business transactions during the preceding year. He has been under active intraspinal treatment; the curve and Wassermann remain unchanged; clinically there has been no change in his condition.

Mr. Y., aged thirty-nine years; infection in 1897. In 1906 had double vision and bladder weakness. In 1912 had tingling in feet, unsteadiness in gait, and great fatigue. He has absent knee-jerks and a Charcot joint of the right hip. The latter part of 1914, according to his family, he was depressed and very forgetful. A spinal-fluid examination made after he had had intensive intravenous and mercurial treatment showed: cells, 2; globulin, + +; Wassermann, + + + + to 0.6. A gold sol test made in May, 1915, read 5555432200.

Mr. Z., aged twenty-seven years. Chancre eight years ago followed by secondaries of the skin and mouth. Treatment internally until 1910, when he developed paralysis of the left external rectus. December 20, 1912, station and gait normal; knee- and ankle-jerks hyperactive; coördination perfect; no sensory changes; objectively viscera normal; pupils normal. Complains of shooting pains in legs, tingling and cramps in calves. Blood Wassermann ——.

Spinal-fluid examination in December, 1913: cells, 26; globulin, +; Wassermann, + + + + to 0.4. Colloidal gold test made in May, 1915, and all subsequent ones give a paretic curve. This patient has had, since the latter part of 1913, 30 intravenous injections of salvarsan and 30 intraspinal injections in addition to mercury. His present fluid examination shows: cells, 3; globulin, + + +; Wassermann, + + + + to 0.4. He is of powerful physique, and during the time he has been under treatment has interrupted his work, which is that of a stationary engineer, only for intraspinal therapy. No change in character or personality has been noted.

In analyzing those cases of general paresis which I have had under my care from time to time the striking feature has been the multiform clinical picture, and in many the absence of the chief symptoms of the affection, namely, the typical cerebral disorders, as writing and speech defects, tremor and memory defects. Some of the patients have had simply a convulsion or two or fainting attacks, while a few others have exhibited no signs referable to the condition, the diagnosis being based mainly on the persistent positive Wassermann reaction and the gold sol test. While it would be premature to make a definite pronouncement as to the prognostic significance of the paretic curve, we must bear in mind the teaching of postmortem findings that anatomical changes in general paresis may long antedate the clinical manifestation. In patients, therefore, who are under continuous observation, and especially those who are receiving intraspinal treatment when the fluid can be examined at regular intervals, the presence or the development of the paretic curve should excite a strong suspicion that these patients may later develop the clinical syndrome. My procedure with these patients is to advise the family or business associates of the possibilities in the case, especially when large business interests are involved, and to treat these cases intensively with the hope that we may anticipate perhaps, retard or arrest, the degenerative cerebral changes. In the type where the meningovascular changes are preponderant, as evidenced by a high cell count, the prognosis is more favorable than where the parenchyma is chiefly involved.

The colloidal gold test has been uniformly positive in all cases with the clinical earmarks of general paresis. In several cases under intensive treatment the paretic curve has changed to the luetic curve. In early syphilis of the central nervous system, *i. e.*, in the early secondary period, I have in several instances found the luetic curve with a negative Wassermann, the only other abnormalities being a slight increase in globulin and lymphocytes. Clinically, these cases gave objective evidence of implication of the central nervous system.

In estimating the number of individuals with abnormal spinal fluids in the secondary stage of the infection I have frequently expressed the conviction that no larger percentage showed definite changes than later developed frank symptoms referable to the neural axis. Further experience strengthens this conviction. In a series of cases examined two years ago abnormalities were demonstrated in less than 20 per cent. In a series of 63 cases recently punctured 10 showed very slight changes as to lymphocytosis and globulin content, coming well within the border-line cases, while 15 exhibited a definite increase in cells and globulin with a positive Wassermann in 7. The cases were all within the first year of infection, untreated or practically so. The standard used was a cell count over 5, a globulin content demonstrated by the Pandy test, a positive Wassermann with 2 c.c. or less of fluid and the color changes elicited by the Lange test. Statistics in the literature treating of abnormal fluids in the secondary stage of lues are variously quoted at from 10 per cent. to 90 per cent. In attempting to reconcile such an apparent disparity it is possible that too much significance has been attached to minor changes, as increased pressure, increase of a few cells, or a trace of globulin. These are probably only transient conditions and part of the systemic infection. My belief is that only such individuals who show very conspicuous changes, as evidenced by a definite cell count, globulin, and positive Wassermann, are candidates for one or the other of the different clinical types of cerebrospinal syphilis. Whether we invoke special conditions as a particular strain or individual predisposition as necessary corollaries to infection of the central nervous system the deduction is forced upon us that in a large majority of patients the organisms must be destroyed spontaneously or by therapeutic agents administered in the ordinary way. The proportion of syphilitics who develop disease of the nervous system is given at from 9 per cent. to 25 per cent. These figures it must be borne in mind were compiled before the era of laboratory diagnoses and their accuracy cannot pass unchallenged.

Treatment. In discussing the treatment of syphilis there are certain general considerations in regard to the therapeutic armamentarium worthy of mention. The object of any energetic antiluetic treatment is the destruction of the greatest number of spirochetes in the shortest possible time. From our knowledge of the immunological and pathological processes in the disease this is best accomplished in the early stage, and from experience accrued during the past five years is more readily and more certainly brought about by the combination of salvarsan and mercury. It has been amply demonstrated that salvarsan is essentially a spirocheticide which, while it has very little influence on the organisms in the test tube, is actively germicidal *in vivo*. Mercury is the best-known germicide *in vitro*. When employed experimentally in animals infected with trypanosomiasis or relapsing fever it is practically inert as far as its effect upon the organisms is concerned and the fatal termination of these diseases is not delayed. In spite of this negative evidence, however, it has been demonstrated empirically for many years that mercury has a curative effect in syphilis, and since the cure depends upon the more or less complete saturation of the patient with the drug its action is presumably a direct one. Nor has it been shown that the iodides are spirochetotropic in their action. Potassium iodide has no effect on the early lesions of syphilis and only a neglible one in rendering the Wassermann reaction negative. It has, however, a profound physiological effect aside from its specific therapeutic action. The latter, in gummata, has been explained by Jobling[4] as due to the neutralization of the antiferments which prevent autolysis and absorption of the necrotic tissue, at the same time rendering the infecting organisms which had previously been protected by the necrotic tissue accessible to the parasiticide.

Salvarsan, by virtue of its spirocheticidal properties, finds its greatest field of usefulness in primary and secondary syphilis when the organisms are abundant. In the later stages, when they are few in number and the tissue changes are more marked, one would naturally expect less results from this agent. As a matter of fact, in gummatous and periosteal lesions and all the active manifestations of late syphilis the therapeutic effect of the drug is almost as intense as in the early contagious period. This is especially true of patients who have been treated over a long period of years with mercury and potassium iodide and have become more or less immunized to the action of these drugs. I have seen patients with periosteal lesions and febrile attacks and numerous cases of so-called malignant syphilis in whom mercury and potassium iodide were practically inert very quickly respond to salvarsan. The following case is a typical example:

Woman, aged forty-two years; infection eleven years ago. Treatment for three years by mouth and injections. When seen September 7, 1915, she was suffering from periostitis of the right parietal and frontal bones, of the sternum and right shoulder. For several months she had been running an evening temperature of 101° to 101.5° F., with headache. During this time mercury and potassium iodide were administered without effect. On September 9, 1915, she was given 0.25 gm. salvarsan. Her pains, headache, and fever disappeared in two days, and there was a most marked general improvement. Since that time she has had six small doses of salvarsan and two of neosalvarsan, and has gained over thirty pounds in weight.

While it is possible, theoretically, to formulate a method of treatment in the various stages of syphilis, as a matter of practice the best devised plan must preëminently be an elastic one, subject to the modifications called for by the susceptibility of the patient to the drugs and to intercurrent reactions which take place from time to time.

[4] Arch. Int. Med., xv, 1915, p. 286.

In early active syphilis, salvarsan alone has been followed by neurorecurrences and monorecurrences or early tertiary lesions. In cases of initial lesion seen before the Wassermann reaction is positive salvarsan may perhaps be given without such danger. It is better, however, not to rely on this drug alone to establish a complete cure but to give the combined treatment. It has been claimed by Wechselman that such combination was more apt to produce kidney involvement, but this contention has not been substantiated by the majority of observers. My own plan is to give a course of mercury with the salvarsan, the number and size of doses of both agents depending upon sex, body weight, and general condition of the patient.

The salvarsan is given in courses of five or six injections in doses of 0.3 gm. to 0.5 gm. for men and 0.25 to 0.4 gm. for women at intervals of one week to ten days. The mercurial injections are given every day or every alternate day if a soluble salt is employed, or once a week if an insoluble one. My preference in case of the former is the bichloride of mercury in courses of twenty to thirty injections given daily or every other day. Of the insoluble preparations, gray oil, (in the form of mercurial cream), of which 5 minims represent one grain, in series of ten to twelve injections, or salicylate of mercury (40 per cent. suspension) in dosage of 1 to 3 grains gradually increased, ten to twelve injections constituting a course. Both salvarsan and mercurial courses are followed by a rest period of six weeks and then the procedure is repeated. Wassermann tests are made periodically, but treatment is not interrupted because of a negative reaction until the adequate amount of medication has been given.

When visceral lesions are present salvarsan should be used in small doses repeated at intervals determined by each case. In cardiac conditions it is better to precede with mercury or mercury and potassium iodide. They are greatly benefited by the latter drug. I have given salvarsan in these cases without untoward symptoms. Whatever form of treatment is decided upon it is important to carry it out persistently. The progress of any active condition can be checked, but anatomical changes like sclerosis or aneurysm are of course permanent.

In primary syphilis before the Wassermann has become positive it is possible to abort the infection both clinically and serologically. While in the past this has been accomplished in some cases with a minimum amount of treatment, such patients now receive two courses each of salvarsan and mercurial injections.

In secondary syphilis with a positive Wassermann it is frequently necessary to give three courses of salvarsan with mercury before the desired effect on the serum reaction is obtained.

In tertiary syphilis the method of treatment depends upon the tissues or organs involved. It is of advantage to combine the courses of salvarsan with intramuscular injections of mercury and to follow this with the prolonged use of potassium iodide and mercury in the form of mixed treatment.

In so-called latent syphilis the administration of salvarsan alone often fails. I have a number of cases in whom the Wassermann reaction continued to show complete inhibition after repeated courses. In many individuals with a positive serum when the nervous system is not involved, careful examination may reveal an aortitis, interstitial glossitis, or the remains of a hepatitis or other viscereal lesion with residua sufficient to call forth a Wassermann reaction. It often requires the most painstaking care to reveal the possible location of the disease. For instance, the nervous system may be implicated and only manifested by slight pupillary irregularity or a slight change in the knee-jerks which might easily be overlooked unless the examination is made by a carefully trained clinician. The spinal fluid should be examined when these deviations are indicative of involvement of the cerebrospinal system, and in all cases with a persistent blood reaction when a focus cannot be determined in the skin, mucous membranes, or viscera. Even in the absence of signs pointing to such implication a Wassermann which does not respond to therapy is an indication for lumbar puncture. More benefit is derived in latent lues from the old-fashioned mixed treatment—that is, a combination of mercury and potassium iodide in a liquid menstruum—than from salvarsan alone or combined simply with potassium iodide. With mixed treatment I have in many instances accomplished the reversal of the Wassermann which had remained persistently positive under salvarsan and mercury.

From Stühmer's[5] experiments the greater part of salvarsan introduced intravenously is stored in the lungs, liver, and spleen in about equal quantities. These form depots from which the drug reaches the circulation, most of it probably passing unchanged through the kidneys and intestines. From the latter a sufficiently large amount is excreted, so that if intestinal disturbance is present marked toxic oxidation products are produced which, when absorbed, may lead to severe reactions.

The reaction following the use of salvarsan may be divided into immediate and delayed.

1. *Immediate.* The commonest symptoms are flushing of the face, cyanosis, a sense of fulness in the head, and precordial distress with slight dyspnea. They usually come on during the administration and may be regarded as anaphylactoid in character. They last but a few minutes and many patients complain of feeling weak or enervated for the next day or two. More rarely patients are met with in whom vomiting occurs during the administration. In a case under treatment this takes place after 15 or 20 c.c. of the solution are introduced. When the attack has passed off the remainder of the

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[5] Arch. f. Derm. u. Syph., cxx, 1914, p. 589.

dose is taken without trouble. A psychical element is probably present in this case. Occasionally attacks of severe pain in the lumbar region come on during the flow of the drug and necessitate its interruption. After half an hour or so it passes off, the patient experiences no further inconvenience, or he may after an hour or more have a chill with temperature and vomiting. These reactions usually come on after several injections have been given.

2. *Delayed.* The symptoms appear after twenty-four hours, three days, or longer. Those after twenty-four hours are usually gastro-intestinal, preceded by a chill or chilly sensation, and are characterized by vomiting and diarrhea with a temperature. In another type there is simply malaise for a few days and then the patients become actively ill with vomiting, fever, and a rash or jaundice, the latter the result in all probability of the action of the arsenic on the liver cells. Rarely suppression of the urine is encountered, and this may be attributable to the direct action of the drug on the renal vessels.

As the majority of the reactions come on only after several doses have been given, one should be warned by their occurrence and regulate the interval and dosage accordingly. In cases in which a dermatitis has been present the drug should not be repeated within six months or a year. I have seen death follow in a patient in whom the significance of such a rash was disregarded during intensive treatment with neosalvarsan. The injections were continued and a most extensive exfoliative dermatitis developed, ending fatally. In my own experience there have been two deaths which may be said to have been directly attributable to salvarsan. In the first, a man, aged forty-two years, the infection was nine years old. For this he had had treatment at intervals for six years. When seen he presented a tubercular ulcerating syphilide of the face, scalp, and left arm. He was given mixed treatment, under which the eruption disappeared. On December 30, 1914, he received 0.35 gm. salvarsan, January 11, 1915, 0.4 gm., January 22, 0.4 gm. After the last treatment he had a slight reaction and a change was made to neosalvarsan, 0.6 gm., on February 10, 1915, which was repeated February 20, 1915. Three days later he developed a temperature of 102° to 104° F., and a generalized dermatitis which partially subsided after a week and then recurred with increased intensity. It involved the entire cutaneous surface, the integument became thickened, leathery-like in consistency, and pigmented. After a few days abscesses developed in various parts of the skin followed by a recurrence in temperature and rapid heart action. These abscesses were opened and drained, but in spite of all the care which could be given the patient death ensued. In this case death could be primarily ascribed to the salvarsan dermatitis and secondarily to the sepsis which followed the cutaneous involvement. The urine showed on March 13 a marked trace of albumin with a few blood and pus cells and a few epithelial casts. On the twenty-third only a trace with a few hyalin casts. It should be added that the patient was markedly alcoholic.

In the second case a woman at the City Hospital, treated in 1911 for an early malignant infection, after the second dose developed suppression of the urine, marked reduction of the blood pressure, vomiting and collapse within twenty-four hours after administration. Autopsy made by Dr. Larkin revealed degenerative changes in the kidney epithelium, in the suprarenal bodies and fatty degeneration of the liver cells.

As mercury has a great affinity for the renal cells the kidney is one of the prime organs to suffer in mercurial intoxication. Hence it is important in the administration of the drug to determine the renal eliminating function and to examine the urine from time to time. From their studies of the various preparations of mercury Schamberg, Kolmer, and Raiziss[6] concluded that the toxicity of the different salts is proportional to the amount of pure mercury contained. After absorption the drug circulates about as a compound of mercury albuminate and sodium chloride, excretion taking place chiefly in the feces and only to a small extent in the urine. It is believed that a definite ratio is maintained between the amount excreted by the kidneys and that present in the general circulation and passing through the renal vessels. The rapidity with which it appears in the urine is taken as an indication of the rapidity and intensity of its effects in the body, its elimination corresponding with its cessation of activity. Its excretion continues for months, and it may appear again after the urine has become free, from which it is deduced that mercury is stored up in the different organs and unless elimination keeps pace with absorption poisoning will result.[7]

When inunctions are employed mercury appears in the urine from the first day on. Elimination gradually increases to a certain point, then remains for weeks nearly constant, and after cessation of treatment falls again gradually.[8] The method is very efficacious, but, unless in the hands of a professional rubber, uncertain. Its disadvantages are constant supervision and filthiness.

When given orally the amount of mercury in the urine shows marked variations from day to day, due apparently to varying conditions affecting absorption from the intestine. With suddenly increased absorption there is danger of mercurialism.[9]

The results of the treatment of syphilis by intramuscular injections of mercurial salts are more rapid after the use of a soluble than an insoluble preparation. The soluble salt is more rapidly efficacious because it is possible to more quickly mercurialize the patient owing to the more rapid absorption and less local reaction. Excretion begins at once, and if given each day elimination rises gradually and regularly, the amount gradually decreasing when stopped. Unfortunately, to be efficient, the injections should be given daily in doses of $\frac{1}{10}$ to $\frac{1}{5}$ grain. This, of course, can be done in hospital wards where patients are under continuous observation, but in dispensary practice and private work it is found to be impracticable because of the frequent visits necessitated. For this reason the insoluble salts have come into use. They form a depot of absorption and require to be administered only at weekly intervals. The rate of absorption is of course much slower, the local reaction more intense and the therapeutic effect slower and less reliable. From animal experiments Schamberg, Kolmer, and Raiziss found that at the end of six or seven weeks almost 50 per cent. of the mercury of insoluble preparations may be unabsorbed at the site of injection. Cases have been reported in which patients weeks or months after treatment suffered from mercurial poisoning when sudden absorption from several foci took place. The elimination curve does not indicate a gradual regular saturation, but maximal elimination occurs on the day of injection and sinks immediately, rising with each new injection. We are now treating all of our cases at the City Hospital with soluble preparations, and we find that some of the most refractory rashes, like the early follicular syphilide, disappear in from two to three weeks even when salvarsan is not given. They are also especially valuable in cerebrospinal syphilis when a rapid effect is desired.

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[6] Jour. Cutan. Dis., xxxiii, 1915, p. 819.

[7] Meyer and Gottlieb, Pharmacology; Clinical and Experimental.

[8] Ibid.

[9] Ibid.

Conclusions. The fate of the syphilitic individual depends upon the early diagnosis of his infection and the intensity with which treatment is carried out in the first six months. In the accomplishment of this purpose the modern aids to diagnosis have rendered great service. The dark-field illumination furnishes a valuable means of corroboration in all suspicious genital sores and assists in determining the nature of extragenital lesions which may simulate chancre. It should be employed in every case of chancroid to confirm or rule out the possible coincident infection with the Treponema pallidum.

The Wassermann test fills a large field of usefulness not only as a diagnostic medium but as a guide to the effect of treatment and criterion of cure. It is of special value in all conditions of obscure etiology referable to the cardiovascular system, cerebrospinal system, or viscera in which syphilis might be a factor, and in cases with an indefinite clinical picture, such as neuresthenia, febrile attacks, rheumatic pains, etc. Its interpretation is of great importance and requires as much training and experience on the part of the practitioner as does the interpretation of the physical signs.

The examination of the spinal fluid enables us to determine the activity of the luetic process in the brain or cord, to distinguish the various pathological types affecting the central nervous system, and in many cases to differentiate between these and non-syphilitic affections. Recent investigations have shown that an analysis of the spinal fluid is not complete unless the Lange or colloidal gold test is performed in addition to the Wassermann reaction and a cytological and chemical examination. Its chief usefulness lies in distinguishing true paresis from types of cerebrospinal syphilis which simulate it and in diagnosing incipient cases before the clinical syndrome is established. This affects chiefly the prognosis, as our main hope lies in the early diagnosis and treatment of these cases, for when degenerative stigmata are already present the outlook is not so encouraging, for sooner or later relapses occur.

In primary syphilis where the spirochetes are demonstrated and the Wassermann reaction is negative it is possible to cure syphilis with salvarsan alone. It cannot be determined how many doses are required, and as there may be a dissemination of spirochetes even in the presence of a negative Wassermann reaction it is better, therefore, to err on the side of safety and to give at least eight to ten doses and follow this with mercury for perhaps six months.

In secondary syphilis when the early rash is present and the Wassermann positive it is better to precede the salvarsan with several injections of a mercurial salt, preferably a soluble one, on account of the economy of time. In this way an effect is produced on the spirochetes, and when salvarsan is given the temperature reaction and an intensification of the rash—that is, a Herxheimer reaction—can be avoided. After the salvarsan is begun the treatment is to be continued in the manner outlined in the body of the article. The dermatologist and syphilologist should keep in mind the possibility of the involvement of the nervous system in secondary syphilis, and a complete status should be made when the patient comes under observation so that this record can be compared with any subsequent developments. In this way we are often enabled to detect the very earliest changes which manifest themselves objectively in the nervous system. The most frequent are irregularity of the pupils, persistent headache, and optic neuritis, or auditory disturbance.

In latent syphilis with a positive Wassermann reaction an investigation should be made of the cardiovascular and of the nervous systems or of previous involvement of any of the viscera, as, for instance, syphilitic hepatitis. In cardiovascular syphilis the prolonged use of mercury in connection with potassium iodide is probably of more value than the haphazard use of occasional doses of salvarsan. In other words, in tertiary syphilis with a persistent positive Wassermann reaction without involvement of the central nervous system the beneficial effects of potassium iodide cannot be too strongly insisted upon. In bone and periosteal lesions attended by severe pain there is no drug in the Pharmacopœia that produces so rapid an effect in relieving the pain and reducing the neoplasm.

The criteria of cure are a negative Wassermann reaction for at least a year continuing so after a provocative injection of salvarsan and a normal spinal fluid, with the exceptions which have been noted.

TABLE I.—RESULTS OF TREATMENT IN CASES OF EARLY INFECTION.

Case.	Duration of infection.	Treatment.							Serological result.	Clinical or serological relapse.	Provocative salvarsan.
		Begun.	Ended.	Amount and kind.							
				Salvarsan injections.	Mercury.			Mixed.			
					Injections.	Rubs.	Oral.				
J. M.	2 months	July 15, 1910	July 25, 1911	1	19	35	3 months	. . .	June 9, 1911 –	None	June 24, 1914 –
G. S.	9 weeks	Feb. 2, 1911	Oct. 1, 1913	2	. .	60	3½ months	. . .	Dec. 6, 1911 –	"	Dec. 17, 1913 –
C. E.	2 months	Feb. 11, 1916	Sept. 15, 1912	2	One and a half years			. . .	April 26, 1911 –	"	June 17, 1914 –
W. C.	2 months	Nov. 17, 1910	Dec. 22, 1910	3	. .	. .	. .	. . .	Feb 4, 1911 –	"	Dec. 23, 1914 –
H. N.	2 weeks	Nov. 20, 1911	July 9, 1912	4	17	. .	. .	. . .	Oct. 6, 1912 –	"	Mar. 28, 1914 –
B. S.	10 weeks	Nov. 24, 1913	Dec. 19, 1914	17	47	. .	. .	. . .	Sept. 14, 1914 –	"	Dec. 6, 1915 –
A. N.	7 months	Sept. 27, 1913	Sept. 9, 1914	17	41	. .	. .	. . .	Oct. 9, 1914 –	"	Dec. 28, 1915 –
J. G.	6 weeks	Feb. 19, 1908	Oct. 21, 1910	. .	31	. .	1 year	1 month	Jan. 25, 1911 –	"	Feb. 26, 1915 –
S. W.	6 weeks	Dec. 30, 1910	July 27, 1911	2	13	10	. .	. . .	June 11, 1913 –	"	
R. Y.	3½ months	Jan. 14, 1911	July 9, 1912	7	. .	. .	. .	. . .	Mar. 11, 1911 –	"	
G. B.	5 weeks	April 10, 1911	Jan. 15, 1912	3	. .	9 weeks	2 months	. . .	May 4, 1912 –	"	
T. C.	1 month	Oct. 21, 1912	Nov. 9, 1912	4	. .	. .	. .	. . .	Always –	"	
H. C.	4 weeks	Jan. 23, 1914	Oct. 30, 1914	10	21	. .	. .	. . .	April 18, 1914 –	"	
G. C.	5 weeks	July 31, 1914	April 14, 1915	10	24	. .	. .	. . .	Nov. 18, 1914 –	"	
C. A.	6 weeks	Dec. 15, 1913	Oct. 17, 1914	6	25	. .	. .	. . .	Always –	"	
J. C.	2 months	June 13, 1914	Mar. 2, 1915	9	25	. .	. .	. . .	Sept. 17, 1914 –	"	
H. N.	4 months	Nov. 16, 1913	May 29, 1914	13	13	. .	. .	. . .	May 27, 1914 –	"	
R. G.	8 weeks	Aug. 16, 1913	June 2, 1914	12	19	. .	. .	. . .	June 13, 1914 –	"	
W. C.	6 weeks	Aug. 15, 1905	Oct. 6, 1909	. .	50	. .	7 months	6 months	Oct. 24, 1913 –	"	

TABLE II.—RESULTS FOLLOWING PROVOCATIVE INJECTION.

Case.	Date of infection.	Wassermann before treatment.	Treatment.						Wassermann.	Clinical or serological relapse.	Provocative salvarsan.
			Begun.	Ended.	Amount and kind.						
					Salvarsan injection.	Mercury.					
						Injection.	Rubs.	Oral.			
P. A.	1886	4 +	Dec. 2, 1909	June 18, 1912	1	61	. . .	. . .	Dec. 6, 1913 –	None	Jan. 14, 1914 + + + +
J. B.	1897	(?)	1897	1900	. .	. . .	. . .	2½ years	Oct. 30, 1912 –	"	Nov. 12, 1912 + + + +
C. M.	1910	(?)	Oct. 19, 1914	Feb. 1, 1915	. .	50	. . .	. . .	April 3, 1915 –	Has tabes	April 14, 1915 + + + +
J. A.	1901	(?)	1901	1905	. .	1½ years	3 years	. . .	Mar. 15, 1916 +	Gummata	Mar. 23, 1916 + + + +
E. K.	Hereditary, 7 years old	+	No treatment Parents syphilitic	No symptoms	. .	. .	. . .	. . .	. . . .	. . . .	Provoc. KI Oct. 7, 1915 Wassermann Mar. 1, 1916 + + + +
J. C.	1890	(?)	1890	1899	. .	. .	8 years	6 months	1909 –	None	Jan. 23, 1912 –
W. H. S.	June, 1913	4 +	Dec. 2, 1913	Oct. 1, 1914	16	44	. . .	. . .	Nov. 24, 1914 –	"	Sept. 12, 1915 –
T. P.	(?) third stage	4 +	Sept. 29, 1913	April 11, 1914	16	42	. . .	. . .	May 11, 1914 –	"	Oct. 20, 1915 –
J. E. H.	Feb. 2, 1914	4 +	April 14, 1914	Dec. 1, 1914	16	38	. . .	. . .	Jan. 25, 1915 –	"	Nov. 27, 1915 –
S. D.	(?) third stage	4 +	Sept. 24, 1913	Sept. 15, 1914	17	49	. . .	. . .	Oct. 16, 1914 –	"	Feb. 9, 1916 –
G. E. G.	(?) third stage	4 +	May 19, 1914	July 9, 1915	13	56	. . .	. . .	July 9, 1915 –	"	Dec. 20, 1915 –
M. R.	May, 1914	4 +	July 8, 1914	June 15, 1915	15	46	. . .	. . .	Feb. 3, 1915 –	"	Dec. 19, 1915 –
B. S.	Miscarriages	4 +	Dec. 26, 1913	Feb. 30, 1915	19	47	. . .	. . .	Mar. 2, 1915 –	"	Feb. 7, 1916 –
B. S.	Sept., 1913	4 +	Nov. 24, 1913	Dec. 1, 1914	17	47	. . .	. . .	Sept. 14, 1914 –	"	Dec. 6, 1915 –
C. B.	April, 1914	4 +	Dec. 29, 1914	Dec. 15, 1915	15	45	. . .	. . .	July 22, 1915 –	"	Feb. 8, 1916 –
A. N.	Jan., 1913	4 +	Sept. 27, 1913	Sept. 9, 1914	17	51	. . .	. . .	Oct. 9, 1914 –	"	Jan. 24, 1916 –
A. Mc.	May, 1914	4 +	July 12, 1914	July 15, 1915	17	42	. . .	. . .	Feb. 15, 1915 –	"	Jan. 3, 1916 –
T. M.	1908	4 +	Oct. 21, 1912	July 7, 1913	9	22	. . .	. . .	Sept. 11, 1913 –	"	Dec. 27, 1915 –

TABLE III.—INTRACTABLE REACTIONS AFTER PERSISTENT TREATMENT.

Case.	Date of infection.	Wassermann before treatment.	Treatment.					Wassermann after treatment.	Clinical relapses during treatment.	Remarks.
			Amount and kind.				Duration.			
			Salvarsan injections.	Mercury.		Mixed.				
				Injections.	Rubs.					
W. Z.	Nov., 1911	++++	14	45	...	....	$1\frac{1}{2}$ years	++	None	Clinically negative.
B. H.	April 26, 1913	++++	16	36	...	....	1 year	+	"	Clinically negative.
F. G.	April, 1912	++++	20	26	...	....	$1\frac{1}{2}$ years	+	"	Clinically negative.
A. R.	1909	++++	22	36	4 months	4 months	2 years	++++	"	Clinically negative; spinal fluid negative.
W. W.	1899	++++	16	31	...	8 months	$2\frac{1}{2}$ years	++++	"	Has remains of hepatitis.
L. H.	Dec., 1912	++++	15	101	4 months	18 weeks	$2\frac{3}{4}$ years	++	"	Has aortitis.
I. D.	Mar., 1913	++++	12	72	...	6 months	$2\frac{1}{2}$ years	+	"	Has aortitis.
J. B.	Denied	++++	17	10	...	6 months	$1\frac{1}{2}$ years	++++	"	Large aneurysm present.
R. H.	1907	++++	23	30	88	16 weeks	2 years	++++	"	Optic atrophy; spinal fluid positive.
F. M.	1903	++++	9	32	...	....	7 months	++++	"	Tabes; spinal fluid positive.
G. M.	1902	++++	20	60	6 months	1 year	$2\frac{1}{2}$ years	++++ ++++	"	Spinal fluid positive; cerebrospinal syphilis.
E. R.	1904	++++	31	40	...	....	$1\frac{1}{2}$ years	++++	"	Has paresis; spinal fluid positive.
M. D.	Congenital 29 years ago	++++	18	36	...	2 years	3 years	++++ ++++	"	Remains of keratitis; deafness; spinal fluid negative.

THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.[1]

By Homer F. Swift, M.D.,
NEW YORK.

In order to discuss treatment of syphilis of the central nervous system it is essential to orient ourselves in the various problems which this disease presents.

It is now well established that spirochetes circulate in the blood of practically all patients in the late primary and early secondary stages, and during this period the central nervous system is frequently involved. In fact, with the early and almost universal dissemination of the infectious agent it is difficult to conceive how any organ escapes infection. It is not alone the presence of the spirochetes, but the reaction of the tissues toward them which determines the type of infection. It is recognized that spirochetes can lie dormant in the tissues, in latent cases, with practically no cellular reaction about them. Different observers report wide variation in the relative frequency with which the cerebrospinal fluid shows evidence of alteration in the secondary period. Ravaut[2] found abnormalities, with pleocytosis or globulin excess, or both, in 67 per cent. of cases, Altmann and Dreyfus[3] in 66 per cent. Gennerich[4] states that at some time, either before or during intensive salvarsan treatment, 90 per cent. of his cases in the secondary period showed some abnormality of the cerebrospinal fluid. Ellis and I[5] found only 33 per cent. of abnormal fluids in untreated patients in the secondary period, but had the fluids in all patients in the secondary period been included in our statistics the percentage would be somewhat higher.

From the above observations it is evident that infection of the central nervous system occurs in a large proportion of cases of secondary syphilis. Since we know that only a small proportion of syphilitic patients show nervous involvement in later years it is evident that in many cases this infection must undergo spontaneous resolution. This phenomenon corresponds with the course of syphilis elsewhere in the body, and is probably due, in part, to a tissue immunity which develops as a result of prolonged contact between parasite and host. As a result of this tissue immunity the secondary eruption disappears, and cutaneous relapses may never recur even in untreated patients. If, however, cutaneous manifestations do recur they become more and more localized, tend to group, and to involve deeper structures, with finally gummatous changes.

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[1] Read at the Tenth Triennial Session of the Congress of American Physicians and Surgeons, Washington, May 9, 1916.

[2] Ann. de dermat. et de Syph., 1903, S. 4, iv, 1.

[3] München. med. Wchnschr., 1913, lx, 464.

[4] Die Liquorveränderungen in dem einzelnen Studien der Syphilis, Berlin, 1913.

[5] Jour. Exp. Med., 1913, xviii, 162.

A similar process appears to occur in the central nervous system. Following the initial inflammation the organisms deposited in the meninges during the period of spirochetemia are usually destroyed; but in some cases they remain latent only to become active after a period of months or years. This is the usual course of syphilitic infection in untreated or poorly treated cases. The character of the picture may, however, be altered by the institution of intensive treatment. It has long been observed that cases of primary syphilis, relapsing after unsuccessful attempts at abortive treatment with mercury, are liable to show severe skin lesions. Similar deep nodular or ulcerative lesions are frequently seen in the relapses following inadequate salvarsan treatment. This phenomenon of increased severity noted in relapsing lesions of the skin occurs also in the central nervous system, and explains the occurrence of meningitis with cranial nerve paralysis in many of the inadequately treated cases of secondary syphilis. In these patients the greater part of the infecting organisms have been destroyed by the remarkable spirocheticidal action of salvarsan. This has, moreover, been accomplished so rapidly that the usual tissue immunity which develops as a result of prolonged contact between parasite and host is lacking. As a result a small focus of spirochetes, tucked away safely in the tissues of the central nervous system, and thus escaping the spirocheticidal action of the salvarsan can develop in the susceptible host with great rapidity and severity. The severity of the meningitis is evidenced by the cerebrospinal fluid, which shows a marked pleocytosis, considerable globulin excess, and usually a strongly positive Wassermann reaction. The Wassermann reaction in the blood is frequently negative, showing how well the active syphilis is limited to the central nervous system. The failure to recognize this possibility of active meningitis in the early stages of syphilis, with a negative Wassermann reaction in the blood, may result in the failure to resume treatment at a most critical period. It should be emphasized that the development of this condition is due to inadequate intensive treatment, and that a few doses of salvarsan, without continued treatment, may result in more severe nervous manifestations than if milder therapy had been applied.

The recognition of the early involvement of the central nervous system is important not only because of the possibility of the development of an early meningitis but also from the stand-point of prophylaxis of the later and more destructive conditions. The best treatment of brain gummata, tabes, and paresis will always be their prevention.

Before starting treatment in any case it is well to try to recognize the character of the involvement, for the subsequent therapy is, to a certain extent, determined by the type of manifestation. These manifestations depend upon the tissues involved, and upon the reaction of those tissues to the irritative effect of the spirochetes. The disease may implicate the meninges, bloodvessels, or parenchyma. While it is conceivable that any one of these structures may be affected alone, still the intimate relation of one structure to the other makes it almost impossible for one to be diseased without the others sharing to a certain extent in the pathological process. There is, however, a type of nervous disease due to syphilis in which the infection seems to involve the vessels in the form of an endarteritis. In this instance the cerebrospinal fluid shows little if any abnormality, and the symptoms are referable to the arterial sclerosis of the cerebral vessels rather than to actual interstitial or parenchymatous disease. The response of this type of case to treatment depends upon the extent to which the endarteritis can be favorably affected and not upon the resolution of a syphilitic exudate in the meninges.

Following the demonstration of the Treponema pallidum in paretic brains a new classification of lues of the brain and cord has arisen. This comprises (1) interstitial types, which include the lesions previously classified under cerebrospinal syphilis, and (2) parenchymatous types, which include paresis and tabes dorsalis.

In both the interstitial and parenchymatous forms the one common lesion is the perivascularitis which may vary, to a wide degree, from a simple mantling of the vessel to a collection of cells in the form of miliary gumma, and when combined with a similar process in the meninges may result in large gumma formation. In the interstitial forms, which include meningitis, menigo-arteritis, and gumma, the disturbance in function is due either to an actual destruction of the nervous elements or to a cutting off of nutrition to the nerve tracts and centers. This latter condition may be brought about by the narrowing of vessels and compromising of the lymphatic spaces to the edema surrounding active inflammation and to pressure from the tumors. In fact, the remarkable improvement of many of these cases under treatment can be explained only on the basis that the pathological process has been largely limited to the vessels and meninges. In the parenchymatous forms the outstanding picture is degeneration of nervous elements combined with symptoms of irritation of these structures. Unfortunately it is impossible to examine microscopically the tissues in these parenchymatous forms until late in the disease, when the degeneration is far advanced. But even at this time perivascularitis and focal meningitis are usually seen, and it does not seem unreasonable to consider that much of the degeneration is secondary to a disturbance of the nutrition of the cell or axis-cylinder, which has resulted from a blocking of the perivascular, perineural, or perineuronal lymph spaces by the cellular exudate.

In paresis the presence of the spirochete in the brain substance may by the liberation of toxins result directly in the death of the cell. In tabes dorsalis, however, the active inflammatory process is not usually found in the most obviously degenerated areas, namely, the columns of Goll and Burdach, but rather in the dorsal roots and in the meninges surrounding them. An example of the earliest stages of tabes is the interesting case of Larkin[6] in a patient with "sciatica," girdle pains, pleocytosis, and positive Wassermann reaction in the cerebrospinal fluid, who died from a ruptured aortic aneurysm and whose postmortem showed insular sclerosis of the posterior nerve root, with accompanying syphilitic meningitis but no column degeneration.

From the examination of the retina and optic nerves of many cases of optic atrophy in tabetics and paretics, Stargardt[7] concluded that the atrophy is secondary to a round-cell infiltration of the intracranial portion of the optic nerve and the chiasm. In those cases with a segmental optic atrophy there was only a partial infiltration of the optic nerve. He argues against the view that tabetic optic atrophy is a system disease due to a toxin, but believes rather that it is an example of the reaction of the nervous tissue to the spirochete, for in several of his cases the auditory and olfactory nerves were similarly infiltrated. Spiller[8] showed that the essential lesion in tabetic oculomotor paralysis is due to a round-cell infiltration in the oculomotor nerves at their point of emergence from the medulla, which he thinks is probably secondary to the pial infiltration in this region. He considers that the nuclear degeneration is usually secondary to the inflammation of the nerve stem. Thus it appears that the classification of the various tabetic atrophies as primary is only an attempt to explain them in terms of the older opinion that these diseases were parasyphilitic in nature. As a matter of fact, they all appear to be secondary to a chronic syphilitic meningitis.

Chronicity is probably an important element in the development of parenchymatous syphilis. The outstanding symptoms of most cases of tabes or paresis develop from the tenth or twelfth year, after the primary infection. Upon careful questioning of many of these patients it will be found that some single symptom, such as pain or isolated nerve paralysis, often transitory in character, has occurred years previously, and their nature is often recognized only after the disease is well developed. These facts point to the probability that a low-grade inflammation with subsequent atrophy has been going on for years, and only after a sufficient number of tracts or centers are involved to interfere with the patient's usual activities does he seek the aid of the physician. On the other hand, the majority of cases of the interstitial type develop in the first three years after infection. The course is more rapid and the symptoms appear with greater violence, no doubt due to the fact that there is a more extensive and rapid development of the meningeal and perivascular exudate.

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[6] Cited by J. A. Fordyce, Harvey Lectures, 1914–15, Series X.

[7] Allg. Ztschr. f. Psych., 1912, lxix, 735.

[8] Jour. Nerv. and Ment. Dis., 1915, xlii, 15.

In both tabes and cerebrospinal syphilis, then, we are dealing with diseases of a similar nature. The variation in the manifestations seems to depend upon the difference in the rapidity and degree of development as well as upon the localization of the inflammatory process. In tabes the infiltration being less intensive and slower, the picture of degeneration is brought more vividly into the foreground. The spinal fluid in the two diseases is practically the same, even to the type of curve in the gold reaction. Both also respond to specific treatment in much the same manner, although at a different rate, and while the symptoms due to irritation are improved, those due to degeneration are little if any affected.

In paresis, on the other hand, we appear to be dealing with a disease which is not strictly comparable with the two just discussed. There are certain points of similarity, namely, in the meningitis and perivascularitis. The direct action of large masses of spirochetes in the substance of the cerebral cortex may possibly result directly in the destruction of cortical cells and fibers. The peculiar type of curve in the gold reaction, moreover, points to some essential difference between this disease and tabes. The difference in response to treatment is also most striking. While most cases of tabes will show the favorable influence of treatment both in the spinal fluid and in marked and persistent clinical improvement, the response of most paretics to a similar or more intensive treatment is much less noticable, and the ultimate results are usually discouraging. Whether this difference in response is due to difference in accessibility of the active lesion or to the fact that in paresis the disease attacks portions of the central nervous system, which are more essential to the orderly carrying on of vital functions, are questions which are as yet unanswered.

It goes without saying that the best preventive of syphilis of the central nervous system is the prophylaxis of syphilis; but this problem is far from solved. Next in importance is the proper treatment of syphilis in the early stages. It should be emphasized at this point that no case should be released from treatment until the cerebrospinal fluid has been shown to be normal, insofar as pleocytosis and Wassermann reaction are concerned. Whether a slight excess of globulin is an indication for continuation of treatment, if all other abnormal elements are absent, is still an open question. In a number of patients with meningitis in the secondary period, whom we have followed for several years, the globulin is still in excess, although all other evidence of the disease had been absent for three or more years.

Even with the present diagnostic methods and several effective therapeutic agents it is safe to say that a fair proportion of patients with syphilis are poorly treated, and probably a majority of them are released without lumbar punctures. The failure of many patients to be followed until cured is due to several causes: (1) the patients fail to realize the importance of proper treatment in the prophylaxis of later disease and discontinue their treatment of themselves; (2) there is still a surprising lack of facilities in dispensaries for the proper treatment of syphilis; (3) many physicians fail to realize the long systematic course that is required to eradicate the disease completely; (4) there are many cases of innocent syphilis and syphilis with slight, if any, early manifestations which go untreated and later develop serious nervous lesions. (Table I.)

TABLE I.

Mattauschek and Pilcz	Total cases 4134
Developed paralytica dementia	198 = 4.8 per cent.
" tabes dorsalis	113 = 2.7 "
" cerebrospinal lues	132 = 3.2 "
Total	443 = 10.5 "

EFFECT OF TREATMENT.

	None.	1 course.	Repeated energetic
Number of cases	100	134	924
Developed G. P.	25 = 25 per cent.	31 = 23.1 per cent.	30 = 3.2 per cent.
" tabes	11 = 11 "	16 = 11.9 "	25 = 2.7 "
" cerebrospinal lues	3 = 3 "	21 = 15.6 "	71 = 7.6 "

	Poorly treated 1880–84.	Better treated 1895–99.
Number of cases	617	1139
Developed G. P.	60 = 9.7 per cent.	37 = 3.2 per cent.
" tabes	22 = 3.5 "	16 = 1.4 "
" cerebrospinal lues	15 = 2.4 "	28 = 2.4 "

While the incidence of cerebrospinal involvement in syphilis varies in different races and in the different sexes the experiences of Mattauschek and Pilcz[9] is representative. These authors followed 4134 cases of syphilis in officers in the Austro-Hungarian army who were infected between 1880 and 1900. These cases were followed until 1912. The results of these investigations are shown in Table I. A striking feature of the table is the difference in the percentage of cases that developed tabes and paresis who were untreated or poorly treated compared with those who had been energetically treated. Practically a quarter of the poorly treated cases developed paresis contrasted with a little over 3 per cent. of those who were well treated. Similarly from 11 to 12 per cent. of the poorly treated ones developed tabes, while only a fifth of this proportion of well-treated patients developed this disease. A single course of treatment seemed to increase the liability to the cerebrospinal form of lues. This observation is of added interest in view of our present knowledge of the results of insufficient salvarsan treatment on the development of cerebrospinal syphilis already discussed in an early part of this paper. A similar parallelism between early efficient treatment and diminished incidence of tabes and paresis is seen in the last part of the table. In the period between 1880 and 1884 the treatment was relatively insufficient, while in the period between 1895 and 1899 there was an improvement in the general treatment of the disease with a corresponding decrease in the incidence of parasyphilis. It is striking that the incidence of cerebrospinal syphilis in the two groups is the same.

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[9] Ztschr. f. ges. Neur. and Psych., 1910–11, iv, orig., 697; 1913, xv, 608.

If the difference between poor application of mercury and fairly efficient application is so marked it is reasonable to expect that under the modern intensive treatment with both mercury and salvarsan the incidence of parasyphilis should be even more markedly reduced. From a simple, economic point of view the State should provide for the proper treatment of early syphilis, for upon the State eventually falls the cost of caring for the paretic and, to a less extent, for the tabetic.

From the standpoint of prophylaxis of tabes or paresis it is also important to realize that they frequently develop slowly, and that signs or symptoms are often present for years before the disease is fully manifest. Lately more attention has been directed to the monosymptomatic forms of syphilis of the central nervous system. Some authors claim that these forms are more frequent today than formerly, and that tabes is assuming a milder character; but it is more probable that their detection is due to refinement in diagnosis. While fairly numerous cases are reported in which the monosymptomatic forms remained free from further symptoms for many years in spite of lack of treatment it is wiser to regard all such cases as being early forms of late serious disease. Years ago Erb called attention to the importance of ophthalmoplegia interna as a forerunner of tabes or paresis and he has followed several cases from the appearance of a simple eye lesion to the fatal ending in paresis. Many patients with tabes give a history of a transitory squint which was present years before any other symptom. Often the condition has improved after the administration of a small amount of iodides or mercury and the patient has been allowed to escape from further observation. Auditory nerve lesions are also described early in tabes as well as in cerebrospinal syphilis. These patients usually consult the otologist. It is important for the specialist to realize that these isolated nerve lesions are a part of the general disease, syphilis of the central nervous system, and that they are usually manifestations of a basilar meningitis. Surgeons also see early manifestations in abdominal disturbances. Nuzum[10] recently reported that among a thousand cases of tabes admitted to Cook County Hospital, 87 had previously undergone laparotomy because of the mistaken diagnosis of their abdominal pain. It is important to remember that gastric crises, either mild or severe, may be present as the first manifestation of tabes for years before full development of the disease. Other single symptoms which are often present for a longer or shorter period are bladder disturbances, lightning pains in the leg, and "rheumatism." The general practitioner or the specialist should recognize the nature of these symptoms and place the patient under proper treatment, for it cannot be emphasized too strongly that prevention of degeneration is worth vastly more than the treatment of symptoms once they have fully developed.

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[10] Jour. Am. Med. Assn., 1916, lxvi, 482.

The examination of the blood and cerebrospinal fluid is of the greatest help in clearing up the diagnosis in doubtful cases, and to a certain extent in determining the type of syphilitic involvement of the central nervous system. While these examinations are of great value, they do not replace but only complement a careful clinical examination. I cannot do better than quote Miller:[11] "The value and interpretation of any laboratory method should always be based upon the most careful clinical study of the cases in which it is applied;" and also, "Any normal reaction in the cerebrospinal fluid may be present or absent in any luetic involvement of the brain or spinal cord." There are certain combinations of reactions which occur with sufficient frequency in certain conditions to render such findings highly significant. An increase in globulin is found in most cases of any type; it is most marked in paresis, but may be equally intense in secondary meningitis. Pleocytosis is usually the most intense in meningitis in the secondary stage, but counts above 100 are not infrequent in later cerebrospinal syphilis, tabes, and paresis. The type of curve given by the Lange gold reaction in cerebrospinal lues and tabes is of confirmatory value, but its great field of usefulness seems to be in differentiating paralytica dementia from these two conditions. The fact that the fluid from a patient with a clinical diagnosis of tabes, or cerebrospinal syphilis, gives a paretic curve does not militate against the reaction, for it is well known that between 10 and 15 per cent. of tabetics develop paresis, and at time it is impossible to differentiate between cerebral syphilis and paresis. If future observations confirm what now seems probable, namely, that a paretic curve obtained with the spinal fluid of patients clinically not paretic points to a possible development of this disease, it will be of importance in prognosis and of value in determining why symptoms of mental disorder appear in spite of vigorous and prolonged treatment.

At this point it is well to emphasize the value of constant methods in making the various tests on the cerebrospinal fluids. Dilutions for cell counts should be made immediately. The necessity of proper solutions for the gold test have been pointed out by Miller[12] and his co-workers. Of no less importance is the titration of the strength of the Wassermann reaction in the spinal fluid. The designation of + + + + or negative Wassermann reaction in the fluid means but little unless we know the amount of fluid that was used in obtaining these readings. This is especially true when the effect of treatment is being estimated. For example, if 0.2 c.c. or 0.4 c.c. has been the only amount used to test the fluid a relatively mild treatment may change the reaction to negative. On the other hand, if only 1 c.c. has been used a more intensive treatment may not affect the reading, although, as a matter of fact, the reaction may be much weaker. The only way to judge accurately of the effect of treatment on the reaction is to test the fluid with diminishing amounts corresponding to values between 2 c.c. and 0.2 c.c. in the original Wassermann test (smaller amounts if necessary) and determine the point at which the reaction is completely positive. If, then, with a given amount of treatment the positive point has moved from 0.2 c.c. to 0.6 c.c. or higher, we know that the treatment is having some effect. This, of course, presupposes that constant methods are used at different times, for if a very sensitive method is used at one time and a comparatively unsensitive one at another the relative value of the two tests is lost.

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[11] New York State Jour. Med., 1915, xv, 376.

The problem of treatment of syphilis of the central nervous system is complicated by the peculiarities of the subarachnoid space which, in addition to the larger spaces and cisterna, is directly continuous with the perivascular, perineural, and perineuronal lymph spaces. It does not seem unreasonable to suppose that the infection is carried by the cerebrospinal fluid along these channels, and the various meningeal and perivascular lesions can be most easily explained in this way. Frühwald and Zaloziecki,[13] in a review of their own cases and of the literature, have shown that the fluid is occasionally infectious in all stages from the secondary period to tabes and paresis.

The reaction to the spirochete is meningitis and perivascularitis. It is probable that the nerve cells and fibers obtain their nutrition to a considerable degree through these spaces, hence plugging of them with exudate not only compromises the nutrition of these structures but also probably increases the difficulties with which therapeutic agents are brought into contact with the exudate. At present it seems almost superfluous to recite the numerous experiments which prove the separateness of the subarachnoid space from the general lymphatic and blood-vascular systems. Antibacterial immune bodies, vital stains, and most drugs, when administered by mouth or parenterally, do not reach the subarachnoid space in demonstrable quantities. It is true, however, that many drugs, given either by mouth or subcutaneously, do act on the central nervous system, but these drugs administered subdurally act in much smaller quantities. Many years ago Lewandowsky[14] showed that strychnin when injected intraspinally was ten times as effective as when injected intravenously. Similarly, sodium ferrocyanide subdurally was potent in one-hundredth the intravenous dose. The action of both drugs was at first local and then general, showing that they were rapidly diffused through the cerebrospinal fluid.

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[12] Johns Hopkins Hosp. Bull., 1915, xxv, 391.

[13] Berl. klin. Wchnschr., 1916, liii, 9.

In many cases the general administration of mercury, iodides, and salvarsan affects favorably the course of syphilis of the cerebrospinal axis. This favorable influence is especially marked in the early forms of the disease. The tendency, however, of cerebrospinal syphilis to relapse in spite of energetic mercurial and iodide treatment has long been noted by syphilographers and neurologists, and the failure of most cases of tabes to respond to the antiluetic treatment of the presalvarsan era made therapeutic nihilists of most neurologists. Even the brilliant clinical improvement of most cases of cerebrospinal syphilis and tabes after salvarsan intravenously has not been followed by a parallel improvement in the cerebrospinal fluid. Dreyfus,[15] who gives courses of salvarsan of 4 to 6 gms. combined with ten to twelve injections of calomel or gray oil, notes that many such courses are necessary to eliminate all signs of the disease. In only 3 out of 125 cases of cerebrospinal syphilis did the fluid become normal after one or two courses. Gennerich,[16] who is famous for the intensity of his antisyphilitic treatment, says that he feels that all cases with meningeal involvement in any stage should have intraspinal treatment. Many observers report cases of cerebrospinal syphilis or tabes which, having come to a standstill, both clinically and pathologically, under general treatment, have shown renewed improvement under intraspinal therapy.

The desirability of subarachnoid therapy has been well established. The problem was to find some beneficial therapeutic substance which could be repeatedly introduced without injury to the delicate nervous tissue, for only by repeated and prolonged treatment can we hope to arrest any form of cerebrospinal lues permanently. Last year,[17] the writer reviewed the use of these various agents and the methods of their administration. Suffice it to say that the preparations which have stood the test of time are (1) the serum obtained from patients shortly after intravenous injections of salvarsan; (2) serum to which small quantities of salvarsan have been added; (3) neosalvarsan in small quantities and weak concentration, and (4) mercurialized serum.

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[14] Ztschr. f. klin. Med., 1900, xl, 480.

[15] München. med. Wchnschr., 1914, lxi, 525.

[16] Ibid., 1915, lxii, 1696.

[17] Swift, H. F., Jour. Am. Med. Assn., 1915, lxv, 209.

The direct application of mercury in the form of albuminate, as devised by Byrnes,[18] should theoretically be of value, and the reports seem to indicate that if the amount of mercury is kept under the irritating dose, beneficial results may be expected from its injection. It is well to call attention to the danger of repeated injections of mercurialized horse serum, which may lead not only to a general anaphylactic state to horse serum, but may cause the meninges to become hypersensitive to the foreign protein, and repeated injections over a number of months may lead to a chronic meningitis similar to the condition we are trying to combat.

The injection of neosalvarsan in concentrated solutions, as recommended by Ravaut,[19] or even in one pro mille solutions has been proved by numerous observers to be a dangerous procedure, since it is apt to be followed by various degrees of urinary retention and incontinence, rectal paralysis, paresthesia of the legs, ataxia and girdle sensations, and, in severe cases, by paralysis of the lower extremities and death. A given dose may be well tolerated several times, but later be followed by severe symptoms. Because of the uncertainty of unfavorable sequelæ, intraspinal injections of neosalvarsan should be given with extreme caution. Gennerich[20] lately reported that by using very dilute solutions he has been able to avoid these unpleasant symptoms. He, however, warns against the use of more than 0.5 mg. in spinal cord disease and not over 1 or 2 mg. in patients with paresis or syphilitic meningitis. Personally, I feel that repeated doses of this size are dangerous.

The addition of small quantities of salvarsan to serum as recommended by Ogilvie[21] was devised to give a known amount of salvarsan instead of the uncertain amounts in the serum salvarsanized *in vivo*. Marinesco and Minea[22] have noted that neosalvarsan is less irritating when diluted with serum than when dissolved in water or saline. Both Ogilvie and Fordyce,[23] however, have noted bladder disturbance and paresthesia in the legs when more than 1 mg. of salvarsan was added to the serum, and now I recommend that the dose should never be over 0.5 mg., usually less. With these quantities, intraspinal treatment has been followed by distinctly beneficial results.

The use of the serum of patients withdrawn after intravenous salvarsan injections has been criticized chiefly because of the small amounts of salvarsan it contained. We have found that the majority of the sera one hour after an intravenous injection contained 0.01 mg. or more per cubic centimeter. When 12 to 20 c.c. of serum are used each treatment represents the injection of from 0.12 to 0.2 mg. of salvarsan. As above noted it is unsafe to inject intraspinally more than a fraction of 1 mg. of either salvarsan or neosalvarsan. The uncertainty of the dosage is an objection which cannot be overcome unless definite quantities of salvarsan are added.

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[18] Swift, H. F., Jour. Am. Med. Assn., 1914, lxiii, 2182.

[19] Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, xxxvi, 752.

[20] Loc. cit.

[21] Jour. Am. Med. Assn., 1914, lxiii, 1936.

[22] Rev. neurol., 1914, xxii, 337.

[23] Jour. Am. Med. Assn., 1914, lxiii, 552.

The "autosalvarsanized serum" is, however, definitely spirocheticidal and the salvarsan is present in a colloidal combination with the serum which cannot be dialyzed through a celloidin membrane, as can salvarsan alone (Young,[24]). Salvarsan in this colloidal state is probably more slowly diffused out of the cerebrospinal fluid, hence is longer in contact with the syphilitic exudates. Moreover it seems to us that some of the beneficial effect from serum injection may be due to the introduction of the serum *per se*, for[25] we have obtained very interesting results from the intraspinal injection of non-salvarsanized both in diminishing pleocytosis and strength of the Wassermann reaction. The amount of the diminution in the Wassermann reaction is shown graphically in Table II. By reading from above downward the initial strength of the Wassermann reaction is indicated, while the reading from left to right gives the strength after treatment. The original strength of the reaction is also indicated by the heavy blocks. The number of treatments is indicated in parenthesis. It will be seen that 7 out of the 8 cases showed a diminution in the strength of the reaction, and in 3 of them it became negative with 1 c.c. fluid. During the period of observation none of the patients received any other treatment. If two of the cases, *A* and *B*, in which there was little or no effect, the treatment was continued with "autosalvarsanized serum," from other patients, with more marked diminution in the strength of the reaction, as is shown in part two of the chart. The severity of the infection in one of these cases is indicated by the fact that ten months' intravenous and intraspinal treatment was required before the reaction became completely negative. Four other patients were treated with intraspinal injections of salvarsanized serum, and in three of these the reaction became negative with 1 c.c. fluid. A résumé of the results in these 12 cases, treated only intraspinally with either normal or salvarsanized serum, shows that in half of them the reaction became negative with 1 c.c. of fluid, and in the others there was distinct diminution in the strength of the reaction. Two of these patients with gastric crises, Argyl-Robertson pupils, loss of tendon reflexes, bands of cutaneous anesthesia, and loss of deep pain sensation have been observed for over three years without any return of their trouble, and the fluids have remained normal. The results in these cases seem to prove that benefit is derived from intraspinal injections of serum. The explanation of these effects may be and probably is theoretical, but so are the objections to the treatment. The experimental facts stand and the injection of autosalvarsanized serum is followed by fewer permanent unpleasant effects than result from the intraspinal injection of any other antisyphilitic remedy.

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[24] Biochem. Jour., 1915, ix, 479.

[25] The cases reported in this and subsequent tables were treated at the Rockefeller Hospital in collaboration with Drs. Ellis, Chesney and Stillman. A number of them were followed at the Presbyterian Hospital.

TABLE II.—EFFECT OF INTRASPINAL INJECTIONS ON WASSERMANN REACTION IN CEREBROSPINAL FLUID.

Non-salvarsanized Serum.

W. R. before treatment.	W. R. after treatment.								No. of injections.
	++++					--	++++	--	
	0.2 c.c.	0.4	0.6	0.8	0.1	0.1	2.0	2.0	
0.2 c.c.		1 A	....	....	....	....	....	....	8
0.4 c.c.	....	1 B	.	....	....	....	....	....	7
0.4 c.c.	...		1	....	...	....	....	....	13
0.4 c.c.	....			...	1	....	....	....	12
0.6 c.c.	...	....		1	...	. .	...	....	4
0.6 c.c.	.	....		....	...	1	1	....	17
0.6 c.c.	....	....		....	...	1	...	1	6
1.0 c.c.	....	...	....	....		1	...	. .	6
Total 8	...	2	1	1	1	3			

Salvarsanized Serum.

W. R. before treatment.	W. R. after treatment.								No. of injections.
	++++					--	++++	--	
	0.2 c.c.	0.4	0.6	0.8	1.0	1.0	2.0	2.0	
0.2 c.c.		....	1	....	....	...	....	....	12
0.2 c.c.		....	...	....	....	1	....	....	11
0.2 c.c.		....	....	....	....	1	....	....	4
0.4 c.c.	....		1 A	. .	....	. .	....	....	4
0.4 c.c.	....		....	1 B	....	.	....	....	8
0.6 c.c.	....	....		....	....	1	....	....	8
Total 6	....	....	2	1	....	3			

In some patients the pain which follows the injection is so severe that the treatments must be discontinued, but such instances are the exception. The willingness of most patients to return for treatments over long periods is sufficient proof that the method is not too unpleasant for practical application.

A word as to technic: In most of our work at the Rockefeller Hospital the blood was withdrawn one hour after intravenous treatment and the serum diluted to 40 or 50 per cent. with normal saline and injected in quantities of 30 to 40 c.c. of this dilution. It was thought that the dilute serum was less irritating, but for the past two years at the Presbyterian Hospital we have bled the patient one-half hour after intravenous treatment and injected 15 c.c. of whole heated serum without any more reaction than with the older method. Most of the patients now receive both the intravenous and intraspinal injections on the same day and return to their usual occupations the following day. In this way a minimum of time is required. It is necessary to keep some patients in bed for longer periods. In such instances we try to give the treatments on Saturdays so that the patients may be in condition to work by Monday morning.

It has seemed to us that the treatments are better borne if not repeated oftener than once in two weeks. This is especially true in tabetics or patients with spinal syphilis. In paretics or patients with cerebral syphilis the intervals may be shorter. At times it seems wiser to lengthen the intervals. It is well to bear in mind that a certain amount of irritation always follows the introduction of any foreign substance into the subarachnoid space, and the effect of this should be allowed to disappear before the treatment is repeated. A good rule to follow in any form of treatment of cerebrospinal syphilis is not to push the treatment so hard that the patient's general health is depressed. With each treatment there should be some improvement in the general condition; at least there should be no regression; for if a depressing treatment is repeatedly added to a more and more depressed condition the ultimate effect will be injurious rather than beneficial.

The treatment of the several forms of syphilis of the central nervous system presents different problems according to the stage of the disease and the individual patient. One general principle which should always be considered is that in any patient who shows evidence of involvement of the cerebral meninges or brain, salvarsan treatment should be preceded by a short course of mercury to prevent the possible occurrence of a Herxheimer reaction in the region of vital nervous centers. Fortunately such distressing reactions are rare, and can be obviated by proper preliminary treatment. If the presence of gummata is suspected a vigorous course of potassium iodide is often followed by marked improvement. It has seemed to us that the response of cases in the tertiary stage to salvarsan has been more marked and lasting if the courses of salvarsan have followed treatment with mercury and iodides. Gummatous exudates resolve under this preliminary treatment and the spirocheticidal effect of the salvarsan is more readily brought into play.

In the meningitis of the secondary period the response to alternate courses of salvarsan and mercury has been prompt and permanent in all of our cases. Gennerich[26] is of the opinion that all these cases respond more rapidly to combined intravenous and intraspinal therapy, and advises giving two intraspinal treatments after the cerebrospinal fluid has become normal. Following any form of treatment in this condition the cerebrospinal fluid should be examined in two or three months after treatment has been stopped, and every six months for two or more years thereafter to forestall relapses.

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[26] Loc. cit.

In the tertiary forms of the disease the so-called interstitial forms, alternate courses of mercury and iodides, and of salvarsan are usually followed by decided improvement, both clinical and in the condition of the cerebrospinal fluid. If possible the fluid should be examined after each course or each pair of courses. Not infrequently it will be found that the fluid has become normal after a few months' treatment. If so the prognosis is good and treatment should be conducted along general lines. On the other hand if the strength of the Wassermann reaction is the same or only slightly altered after four to six months of intensive general treatment it may be well to resort to intraspinal therapy.

In tabes dorsalis, because of the apparent sensitiveness of many cases to mercury, it is better to start the treatment with small intravenous doses of salvarsan, gradually increasing and giving a treatment every week for a course of six to eight injections. If at the end of this course the Wassermann reaction in the fluid is considerably weaker a course of mercury may be tried, followed by another course of salvarsan, alternate courses being given with periods of rest until the fluid is brought to normal. Many cases will be found, however, in which the strength of the reaction is only slightly altered by such a plan of treatment. The substitution of combined intraspinal and intravenous therapy in these patients will usually result in an improvement in the condition of the fluid. I am convinced that our aim should be to bring the fluids to normal and keep them there if we intend to speak of a cure of the syphilis. That this can be done in a majority of instances is shown in Table III, which gives the results in 37 cases followed for several years. All but 3 of these were tabetics, most of them well advanced. One was a case of diffuse myelitis, one of radiculitis, and one of opthalmoplegia interna. The cases are arranged in groups according to the original strength of the Wassermann reactions in the fluid, and the last finding is indicated in the vertical columns. In 30 of the cases (81 per cent.), the reaction became negative with 1 c.c. of fluid, but in 2 of these the reaction later increased in strength so that the final readings give 28 (75 per cent.) negative. Nineteen of these cases are also negative with 2 c.c., which is double the amount recommended by Hauptmann.[27] Of 18 cases which were negative with 1 c.c. or more, and have been followed from ten months to three and a half years without treatment, 14 remain negative with 2 c.c., 2 remain negative with 1 c.c., but positive with 2 c.c. One relapsed to positive with 1 c.c., and one with 0.6 c.c. In those cases in which the Wassermann reaction of the fluid increased in strength there was also a clinical relapse, while with a single exception in all the cases with persistent negative fluids the disease has not progressed. In this one patient, who showed advanced tabes on admission, there has been an extension of the area of cutaneous anesthesia, and a neuropathic arthropathy of the shoulder joint has developed in spite of a normal fluid and negative blood Wassermann reaction. It will also be seen that there is a certain correlation between the initial strength of the

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[27] München. med. Wchnschr., 1910, lvii, 1581.

TABLE III.—TABES DORSALIS. EFFECT OF TREATMENT ON WASSERMANN REACTION IN CEREBROSPINAL FLUID.

W. R. before treatment.	W. R. after treatment.								Amount of treatment.					
									Before W. R. neg. witn 1 c.c., or until stopped.			Between neg. with 1 c.c.; neg. with 2 c.c. or until stopped.		
	++++					--	++++	--						
	0.2 c.c.	0.4	0.6	0.8	1.0	1.0	2.0	2.0	Mos.	Int. ven.	Int. sp.	Mos.	Int. ven.	Int. sp.
0.2 c.c.		1 ←	①	..	..	..	....	..	12	16	12			
0.2 c.c.		..	1	..	..	..	....	..	7	..	12 ns ss			
0.2 c.c.		..	..	..	1	..	....	..	24	32	15			
0.2 c.c.		..	..	..	..	1	....	..	1	..	4 ss			
0.2 c.c.		..	..	..	..	1	....	1	4	..	11 ss			
0.2 c.c.		..	..	..	..	1 →	→	1	8	12	10	8	10	3
0.2 c.c.		..	..	..	..	1 →	→	1	13	16	16	3	4	4
0.4 c.c.	....		1	..	..	..	....	..	6	..	13 ns			
0.4 c.c.	....		..	1	..	..	....	..	8	15	11			
0.4 c.c.	....		1 ←	←	①	..	....	..	5	..	12 ns			
0.4 c.c.	....		..	..	..	1 →	1	..	11	21	7			
0.4 c.c.	....		..	..	..	1 →	1	..	15	24	18	4	6	5
0.4 c.c.	....		..	..	..	1 →	→	1	12	21	16	24	26	9
0.4 c.c.	....		..	..	..	1 →	→	1	29	35	18	8	8	
0.4 c.c.	....		..	..	..	1	....	1	1½	3	2	cont.		
0.4 c.c.	....		..	..	..	1	....	1	12	14	11	cont.		
0.4 c.c.	....		..	..	..	1	....	1	17	14	29	cont.		
0.6 c.c.	....	..		..	1 ←	①	①	..	6	11	8	8	13	1
0.6 c.c.	....	..		1 ←	←	① →	←	①	..	..	..	8	17	17
0.6 c.c.	....	..		..	..	1	....	..	5	..	8 ss			
0.6 c.c.	....	..		..	..	1 →	1	..	8	18	7	14	26	19
0.6 c.c.	....	..		..	..	1 →	1	..	12	22	16	2	2	2
0.6 c.c.	....	..		..	..	1 →	→	1	8	..	17 ns	9	17	16
0.6 c.c.	....	..		.	..	1 →	→	1	4	6	5	6	9	9
0.6 c.c.	....	..		..	..	1	....	1	2	..	6 ns	4	8	
0.6 c.c.	....	..		..	..	1	....	1	5	8	6	11	21	
0.6 c.c.	....	..		..	..	1	....	1	4	7	..	11	20	10
0.8 c.c.	....	..	..		1	..	....	..	2	5	4			
0.8 c.c.	....	..	..		..	1	....	..	11	15	9			
0.8 c.c.	....	..	..		..	1	....	1	12(3)	20	5			
0.8 c.c.	....	..	..		..	1	....	1	3	6	6	cont.		
1.0 c.c.	....	..	..	..		1	....	..	1	2	2			
1.0 c.c.	....	..	..	..		1	....	..	1½	..	6 ss	cont.		
1.0 c.c.	....	..	..	..		1	....	1	1	2	2	cont.		
1.0 c.c.	....	..	..	..		1	① →	1	1	3	2	cont.		
1.0 c.c.	....	..	..	..		1	....	1	1	2	1	cont.		
1.0 c.c.	....	..	..	..		1	....	1	1¼	..	6 ns			
37	....	1	3	2	3	28	4	19						
....	....	2.7%	8%	5.4%	8%	75%	....	49%						

① = relapse.
ns = normal serum alone.
ss = salvarsanized serum alone.

Wassermann reaction and the amount of treatment which was given before it became negative with 1 c.c. The number of cases in some of the groups is too small for averages to be of value, but in general the 1 c.c. or 0.8 c.c. group required from one to three months, the 0.6 c.c. groups about six months, and the 0.4 c.c. and 0.2 c.c. groups about twelve months. Not infrequently an equal or greater amount of treatment was required to change the reaction from negative with 1 c.c. to negative with 2 c.c.

In the presence of a rapidly advancing case of tabes or of optic atrophy, where it is desirable to arrest the progress of the disease, in an important organ, the institution of combined intravenous and intraspinal therapy at the beginning should be seriously considered, as rapidity of cure is the end to be accomplished.

Compared with the results in other forms of lues of the central nervous system the treatment of paralytica dementia has been disappointing. With the proof of the active syphilitic nature of this disease it was thought that a cure might be expected from intensive treatment; but there is something in the nature of the disease which apparently prevents the remedies from reaching the spirochete in sufficient quantities to eradicate them completely. It is true that most of the cases improve clinically, and in some of them there is a marked improvement in the condition of the spinal fluid. Still, with corresponding amounts of treatment this response is much less marked than in tabes. In addition there is a decided tendency for pleocytosis and Wassermann reaction to increase in intensity when treatment is discontinued. In two of our patients (see Table IV) there was at first almost as marked clinical improvement and diminution in abnormal elements in the cerebrospinal fluid as is seen in tabes. Both have had two relapses, and with each relapse the response to treatment has been less marked. This indicates that as the paretic process grows older it is less amenable to treatment, and probably explains the difference in results from State hospitals for the care of the insane and those from private physicians. In State institutions the cases are usually much more advanced than those which come under the observation of private institutions or practitioners. Thus Runge[28] reports 37.4 per cent. remissions, Raecke[29] 55.4 per cent. improved on salvarsan intravenously, Cotton[30] with combined intravenous and intraspinal therapy 58 per cent. arrested or much improved, and Ogilvile[31] 34 per cent. with complete remissions and 40 per cent. incomplete remissions, a total of 74 per cent. improved. In 4 of Ogilvie's cases both the blood and spinal fluids were brought to normal. When we compare these results with the number of remissions in the presalvarsan era 5.7 per cent.[32] or 7.4 per cent.[33] the treatment of paretics seems justified. The return of a paretic to his business, even though it be for only six months or a year, is often of vital importance to his associates and family. Compared with our therapeutic efforts in chronic cardiac or renal disease the results obtained thus far in paresis are decidedly encouraging, although in none of these diseases can we speak of a cure.

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[28] Deutsch. med. Wchnschr., 1914, xl, 998.

[29] Ibid., 1913, xxxix, 1348.

[30] Am. Jour. Insanity, 1915, lxxii, 125.

[31] Jour. Nerv. and Ment. Dis., 1916, xlviii, 263.

TABLE IV.—PARALYTICA DEMENTIA. EFFECT OF TREATMENT ON WASSERMANN REACTION IN CEREBROSPINAL FLUID.

W. R. before treatment.	W. R. after treatment.							Amount of treatment.		
	++++					−	++++	Mos.	Int. ven.	Int. sp.
	0.1	0.2	0.4	0.6	1.0	1.0	2.0			
0.1 c.c.	1	....	....	...	....	....	....	23(6)	11	8
....	1	....	....	....	....	....	....	18	31	18
....		....	1	....	....	....	....	20	38	26
0.2 c.c.	....		.	1	....	....	....	14	24	24
0.4 c.c.	....	....		1←—	—①	....	....	36(11)	25	21
0.6 c.c.	....	....	....	1←—	——	——	—①	30	50	32

In the treatment of syphilis of the central nervous system we should never forget the patient, and that he may be suffering from disease of other vital organs. If there is marked ataxia, Fraenkel's reëducation movements are useful; if he is emaciated, attention should be directed toward diet and general nutrition. Most patients with this form of disease show a certain amount of mental abnormality. Here psychotherapy is of value. In other words, treatment must be individualized, and while a general plan should be followed in the various forms of the disease, each case may demand a certain deviation to meet the peculiar conditions.

The objects of therapy are threefold: (1) the cure of disease; (2) the amelioration of symptoms; (3) the prolongation of life. With the possible exception of paresis all of these objects may be attained in most cases of syphilis of the central nervous system. To be satisfied with the attainment of the last two without attempting to attain the first is to fail to apply all the means at our disposal.

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[32] Runge, loc. cit.

[33] H. L. Paine, Boston Med. and Surg. Jour., 1913, clxviii, 684.

THE PERSISTENCE OF ACTIVE LESIONS AND SPIROCHETES IN THE TISSUES OF CLINICALLY INACTIVE OR "CURED" SYPHILIS.

By Aldred Scott Warthin, Ph.D., M.D.,

PROFESSOR OF PATHOLOGY AND DIRECTOR OF THE PATHOLOGICAL LABORATORIES IN THE UNIVERSITY OF MICHIGAN, ANN ARBOR.

(From the Pathological Laboratory of the University of Michigan.)

Between the pathologist and the clinician there is always a certain antagonism of attitude with reference to the curability of any given disease. The clinician is, and naturally must be, more or less optimistic as to the results of therapy; and only with the greatest reluctance is he convinced of the weakness or total failure of his therapeutic means and methods. The pathologist, with the opportunities afforded him by tissue examination and autopsy, has the advantage of the very last word; and he becomes pessimistic as to ultimate cure because of his constantly recurring experience of finding evidences of active disease in cases clinically cured. This clash of opinion, clinical and pathological, is not shown elsewhere to such a degree as in the case of the veneral diseases, gonorrhea and syphilis. It took much work on the part of the pathologist to convince the practitioner that clinically cured cases of the so-called "lesser disease" were only apparent cures, and that the gonorrhea-infected individual remained for an indefinite period a germ-carrier, not only dangerous to himself but much more so to his future sex-partner. Likewise in the case of syphilis, therapeutic optimism has in recent years received severe blows at the hands of the pathologist. The frequency of latent syphilis of the heart, aorta, and central nervous system, the demonstration of spirochetes in conditions (paresis, tabes, etc.) until very recently regarded as parasyphilitic in nature and etiology, thus proving these conditions to be still active infections, have somewhat shaken clinical optimism. Cures once promised after a year of active treatment have passed through the two-, three-, and five-year limit, and now some clinicians are advising the syphilitic to take interval treatment over a period of many years or even throughout his lifetime if he will escape the uncertain chances facing everyone who acquires this disease. The wave of therapeutic optimism excited by salvarsan and the negative Wassermann reaction even now is subsiding.

It has been my experience as a pathologist to become very pessimistic as to the curative effects of any of the present-day methods of treating syphilis. Before the spirochete became an absolute pathognostic sign of the presence of this disease, certain myocardial, aortic, and testicular changes were regarded by the pathologist as well-nigh positive proof of syphilis. The practically constant occurrence of these changes in the bodies of cases of clinically cured syphilis gave the pathologist good reason to believe that he was dealing with a still active process, although he had no means of proving this. The pathologist's judgment of these conditions is now confirmed by the demonstration of the spirochete of syphilis in such lesions. Localized tissue lesions of the smallest size and of the simplest nature (fatty degeneration, edema, etc.), that, a few years ago, would not, by any possibility, have been regarded as syphilitic, have been shown to be evidences of the local presence of spirochetes. I have elsewhere urged the fact that our conceptions of syphilis, both pathological and clinical, must be reshaped in the light of the spirochete; and that much work needs to be carried out along this line. The methods for the demonstration of this organism in the tissues should be made a part of the routine autopsy microscopic examination.

In my laboratory we have used Levaditi's original method with great success, and this is at the present time the only method of any value in demonstrating the presence of spirochetes in tissue. Its success will depend in the first place upon the freshness of the tissues. In my experience the spirochetes of syphilis quickly disappear from body tissues after the body becomes cold. Our necessity of having to make autopsies very soon after death has been a very great advantage in this respect. Tissues taken from a warm body within one to two hours after death and immediately fixed in 10 per cent. formol for at least twenty-four hours (better for three days), then put through the Levaditi method and blocked in paraffin give the best results. A formalin neutral in reaction and that has not been kept in wooden casks should be used. When properly prepared the number of spirochetes at times demonstrable in the tissues of congenital and active acquired syphilis is incredibly large. In the case of old latent syphilis the search for the organisms often becomes a prolonged hunt, and much time may be consumed in finding active lesions and demonstrating spirochetes within them. No one should think that this is wholly an easy matter. With an autopsy service of fifty to sixty cases a year the time of one assistant may easily be taken wholly for this work, should histological lesions of syphilis be found only in one-third of these. Such an arrangement I have had temporarily, but even with this advantage, the work has gone slowly enough. It may, however, be greatly expedited by confining the work to the organs, heart, aorta, testicles, and adrenals, most commonly the site of latent syphilis, and by making control blocks of all parts of the organ or tissue for quick survey in ordinary hematoxylin and eosin staining. Should such control blocks show lesions recognizable as those possibly due to the localization of spirochetes, the corresponding block in Levaditi preparation is then examined first before a general examination of all the Levaditi blocks is made. If the blocks taken are small, as they should be, the neighboring Levaditi block is very likely to show some active process also. It may happen, however, that the hematoxylin and eosin sections alone show active lesions. The experiment of removing the paraffin and then putting the remaining portion of the block through Levaditi may be tried, but we have not found this procedure very satisfactory.

In the pathological service of the University of Michigan there were from 1912 to 1914, forty-one autopsy cases (one-third of the adult cases) that on microscopic examination showed active syphilis, determined either by the presence of the spirochetes or by characteristic tissue lesions. In the latter the spirochetes are being demonstrated as fast as the work can be carried out; and this has already been accomplished to such an extent in Class I, all cases in Class II, and in ten cases in Class III (one-half of the latent cases) as to leave no doubt of the correctness of the diagnosis in all of the cases. A preliminary report of this investigation was presented before the Association of American Physicians in 1914, and the publication of this paper has been delayed in the hope that we might be able to demonstrate the presence of spirochetes in all of the "cured" and unsuspected latent cases. This is only half completed. The labor has been much greater than at first anticipated. Six weeks were spent on the heart of one case before a small group of spirochetes was finally found. In eight cases in Class III, my assistant, Miss Wilson, demonstrated spirochetes in the heart muscle, but this work occupied a large part of a year.

The clinical history of a part of these cases gave no suspicion of the existence of a previous syphilitic infection; in others there was a doubtful or suspicious history of the disease; while in a smaller number the patient had been treated, or was at the time of death undergoing treatment, for syphilis. In the majority of cases, it will be seen, the clinical diagnosis, and consequently the treatment, entertained no suspicion of the existence of latent syphilis. In those cases in which syphilis was suspected or diagnosed the treatment in part had been regarded as adequate by the patient and previous physicians, but a new course of treatment had been instituted after coming to the hospital. In a small number of cases the treatment had been more modern; the use of salvarsan had been thoroughly carried out and the case regarded as clinically cured. As the taking of the Wassermann reaction has been made only during the last year a part of the regular examination routine for our hospital cases, it was made in the case of only a small number of those in whom syphilis was unsuspected. In the case of those in whom the infection was suspected or diagnosed it was regularly made. Notes concerning the Wassermann are given with each case.

I have accordingly divided the forty-one cases into three classes:

(1) cases in which there was a known history of syphilis, with treatment regarded as adequate and resulting in a cure; (2) cases in which the syphilitic infection was recognized as still active, treatment being continued; (3) cases in which a syphilitic history could not be obtained or was specifically denied by the patient, the clinical diagnosis not including syphilis and no antisyphilitic treatment given.

CLASS I.—CASES WITH A HISTORY OF RECOGNIZED SYPHILIS, TREATMENT, AND CLINICAL CURE.

1. CASE C.—Age, sixty-two years. Chancre when a young man; treated by physician; never any other symptoms of the disease; apparent cure. No history of alcoholism. Wassermann not made. Clinical diagnosis of enlarged prostate. Operation. Death.

Pathological Diagnosis. Postoperative infection. Chronic purulent pyelonephritis. Old syphilis. Healed gummata of liver and testis. Orchitis chronica fibrosa syphilitica. Chronic epididymitis. Emphysema. Active syphilis in myocardium and aorta.

2. CASE M.—Age, sixty-three years. "Cured syphilis." No symptoms since chancre when a young man. Clinical diagnosis of peritonitis following operation on bladder. No Wassermann.

Pathological Diagnosis. Postoperative peritonitis. Chronic cystitis. Papilloma of bladder. Chronic prostatitis and vesiculitis. Fatty degeneration of all organs. Bronchopneumonia. Latent syphilis in myocardium, aorta and testes.

3. CASE F.—Age, sixty-four years. No history of infection. Treated with mercury. "Cured." Blood gave a positive, and cerebrospinal fluid a negative Wassermann. Clinical symptoms cardiac. Question of aortic aneurism.

Pathological Diagnosis. Mitral insufficiency and stenosis. Aortic insufficiency. Relative tricuspid insufficiency. Chronic parenchymatous nephritis. General atherosclerosis. Chronic passive congestion of all organs. Healed infarcts in lungs and kidneys. Thrombosis. Latent syphilis of heart and testes.

4. CASE K.—Age, forty-nine years (?). Sudden death following fracture of bones of leg. "Cured" syphilis when a young man. Chronic drinker. No Wassermann. Clinical diagnosis of embolism.

Pathological Diagnosis. Fracture of right tibia and fibula. Thrombosis of veins of right leg. Embolus in left pulmonary artery. Fat embolism of lungs. Early stage of alcoholic cirrhosis. Active syphilis in heart and aorta. Advanced syphilitic fibroid orchitis.

5. CASE S.—Age, forty-five years. Chancre when young. Treated. Later tertiary recurrence. Treatment resumed. "Cured." Drinker. No Wassermann. Committed suicide with carbolic acid.

Pathological Diagnosis. Carbolic acid poisoning. Latent syphilis. Saddle-nose. Gumma of spleen. Active syphilis of heart, aorta, adrenals, and testicles. Advanced orchitis syphilitica fibrosa.

6. Case M.—Age, seventy years. Syphilis when a young man. "Cured." Chronic drinker. Clinical diagnosis of uremia. No Wassermann.

Pathological Diagnosis. Chronic parenchymatous nephritis. Chronic prostatitis, vesiculitis, pyelitis, and cystitis. Localized chronic leptomeningitis. Coronary sclerosis. Hypernephroma of right kidney. Active syphilis in aorta, myocardium and testicles.

7. Case R.—Age, fifty-nine years. Date of infection not known. Treated. "Cured." No history of alcoholism. Wassermann negative. No clinical symptoms of syphilis. Clinical diagnosis of tumor of kidney.

Pathological Diagnosis. Hypernephroma of right kidney. Chronic parenchymatous nephritis, prostatitis, vesiculitis, and cystitis. Old tubercles in bronchial nodes. Gummata of spleen and liver. Active syphilis of myocardium, aorta, spleen, liver, and testes.

8. Case L.—Age (?). Syphilitic infection twenty-three years ago. Treated with mercurials. "Cured." Chronic alcoholism. Died of croupous pneumonia. Both blood and cerebrospinal fluid gave a negative Wassermann.

Pathological Diagnosis. Croupous pneumonia. Syphilitic hepatitis. Syphilis of the aorta, heart, adrenals, and testes.

9. Case Mrs. J.—Age, (?) Time of infection unknown. No clinical signs of syphilis. Blood and cerebrospinal fluid gave negative Wassermann. Diagnosis of nephritis.

Pathological Diagnosis. Chronic parenchymatous nephritis. Syphilitic aortitis. Fibroid heart. Chronic cystitis. Emphysema. Chronic vaginitis.

10. Case F.—Age, fifty-four years. Chancre at fifteen years of age. Treated. Never any other symptoms. Moderate drinker. Wassermann negative. Carcinoma of rectum.

Pathological Diagnosis. Adenocarcinoma of rectum. Secondaries in pelvis and peritoneum. General cachexia. Amyloid spleen. Syphilitic contracted kidney. Active syphilis of heart, aorta, and testes.

11. Case G.—Age, forty-five years. Chancre twelve years ago. Treated. "Cured." Wassermann negative. Clinical diagnosis of chronic valvular disease.

Pathological Diagnosis. Aortic insufficiency. Aneurism of ascending aorta. Active syphilitic lesions in heart, aorta, and testes.

CLASS II.—CASES OF CLINICALLY ACTIVE SYPHILIS.

12. CASE W.—Age (?). Date of infection unknown. Blood and spinal fluid gave positive Wassermann. Under treatment for syphilis of central nervous system. Died of pneumonia.

Pathological Diagnosis. Acute purulent bronchopneumonia. Active syphilitic aortitis and meningoencephalitis. Fatty liver and heart. General marasmus.

13. CASE T.—Age, forty-seven years. Denied syphilitic infection. Symptoms of tabes. No history of alcoholism. No Wassermann. Under antisyphilitic treatment.

Pathological Diagnosis. Aictve syphilitic leptomeningitis. Miliary gummata in cord and brain. Diffuse degeneration and sclerosis of cord and brain. Chronic parenchymatous nephritis. Active syphilitic lesions in heart and aorta. Orchitis syphilitica fibrosa.

14. CASE H.—Age, forty-four years. Physician. Accidental infection nine years previously. Blood and spinal fluid gave positive Wassermann. Under active treatment. Early stage of paresis.

Pathological Diagnosis. Syphilis. Paresis. Acute purulent pneumonia. Subacute parenchymatous nephritis. Acute purulent pyelitis. Chronic cystitis. General atherosclerosis. Active syphilitic lesions in brain, cord, heart, aorta, liver, adrenals, and testicles.

15. CASE W.—Age, forty-four years. Had hard chancre when twenty-one years old. Secondaries. Treated. Now shows early stage of tabes. Wassermann positive. Under active treatment.

Pathological Diagnosis. Syphilis. Tabes. Active syphilitic lesions in brain, cord, heart, aorta, liver, and testicles. Acute parenchymatous nephritis. Chronic cystitis, vesiculitis, and prostatitis. Healed tuberculosis of bronchial nodes.

16. CASE S.—Age, forty-five years. Chancre fourteen years ago. Now symptoms of tabes. Wassermann positive. Salvarsan by intraspinal injections. Arsenical poisoning.

Pathological Diagnosis. Syphilis of brain, cord, heart, aorta, pancreas, and testes. Chronic interstitial nephritis.

CLASS III.—SYPHILIS DENIED OR NOT SUSPECTED CLINICALLY.

17. CASE G.—Age, sixty-three years. Denied venereal disease. No history of symptoms of syphilis. No Wassermann. No alcoholism. Clinical diagnosis of prostatic enlargement. Operation.

Pathological Diagnosis. Croupous pneumonia. Early stage of meningitis. Hypertrophy and dilatation of heart. Arteriosclerosis. Chronic parenchymatous nephritis and pyelitis. Chronic cystitis and prostatitis. Syphilitic lesions in heart, aorta, and testes.

18. CASE D.—Age, sixty years. No history of syphilis. No Wassermann. Clinical diagnosis cancer of stomach.

Pathological Diagnosis. Colloid carcinoma of pylorus. Chronic parenchymatous nephritis. Arteriosclerosis. Syphilitic lesions in heart, aorta, adrenals, and testes.

19. CASE MRS. C.—Age, forty-five years. No history of syphilis. No Wassermann. Clinical diagnosis cystadenoma of ovary.

Pathological Diagnosis. Cystadenocarcinoma of ovary. Metastases in liver, spleen, and regional lymph nodes. Syphilitic lesions in heart and pancreas.

20. CASE CO.—Age, forty-three years. No history of syphilis or alcoholism. No Wassermann. Clinical diagnosis of tumor of intestines.

Pathological Diagnosis. Primary lymphosarcoma of intestine. Secondaries in mesenteric and retroperitoneal lymph nodes, kidney, and liver. Chronic parenchymatous nephritis. Fatty cirrhosis of liver. Syphilis of heart, aorta, pancreas and testes.

21. CASE S.—Age, sixty-eight years. No history of syphilis. No Wassermann. No history of alcoholism. Clinical diagnosis of carcinoma of stomach and senility.

Pathological Diagnosis. Active syphilis of brain, cord, heart, aorta, and testes. Early stage of paresis and tabes. Chronic prostatitis. Chronic parenchymatous nephritis.

22. CASE MRS. S.—No history of syphilis. No Wassermann. Dementia.

Pathological Diagnosis. Bronchopneumonia. Syphilis of heart and aorta. Coronary sclerosis. Fibroid heart. Biliary calculi. Adenomatous polyp of uterus.

23. CASE Y.—Age, sixty-six years. Syphilis denied. No history of symptoms. No alcoholism. No Wassermann. Clinical diagnosis of myocardial insufficiency and coronary sclerosis.

Pathological Diagnosis. Active syphilitic myocarditis with cardiac thrombosis. Syphilitic aortitis. Multiple infarction of lungs and kidneys. Chronic parenchymatous nephritis. Early stage of cirrhosis of liver. Syphilitic lesions in adrenals and testicles. Chronic prostatitis, cystitis, vesiculitis, and pyelitis.

24. CASE MRS. WA.—Age (?). Doubtful history of syphilis. Never pregnant. Negative Wassermann. Clinical diagnosis of carcinoma of uterus. Death after operation.

Pathological Diagnosis. Carcinoma of uterus. Recurrence. Postoperative sepsis. Acute parenchymatous nephritis. Syphilitic lesions in heart and liver. Glissonian cirrhosis.

25. CASE MRS. B.—Age, twenty-four years. Treated by previous physician for syphilis. Syphilis excluded in hospital examination. Wassermann negative. Clinical diagnosis of chronic valvular lesions.

Pathological Diagnosis. Active late syphilis. Chronic syphilitic myocarditis and aortitis. Combined stenosis and insufficiency of mitral, aortic, and tricuspid valves. Subacute parenchymatous nephritis. Multiple infarcts of lungs and kidneys. Severe anemia. Fatty liver. Syphilitic ulcer of leg. Gangrenous stomatitis, syphilitic with secondary infection. Colloid goitre.

26. CASE M.—Age, fifty years. No history of syphilis. Negative Wassermann. Clinical diagnosis of thoracic aneurysm and carcinoma of stomach.

Pathological Diagnosis. Carcinoma of stomach. Syphilitic lesions in heart, aorta, and testes.

27. CASE K.—Age (?). Denied venereal disease. Moderate drinker. Negative Wassermann. Enlarged prostate.

Pathological Diagnosis. Medullary carcinoma of prostate. Generalized metastasis. Addison's disease. Hydrothorax. Syphilis of heart, aorta and testes. Subacute parenchymatous nephritis. Chronic catarrhal gastritis. Hydrocele.

28. CASE MC.—Age, forty-four years. No history. Entered in toxic state. Suspected arsenical poisoning. No Wassermann.

Pathological Diagnosis. Acute alcoholic intoxication. Chronic alcoholism. Early stage of fatty cirrhosis of liver. Chronic parenchymatous nephritis. General atherosclerosis. Chronic pachymeningitis. Syphilis of testes.

29. CASE G.—Age, thirty years. Denied venereal disease. Negative Wassermann. Moderate drinker. Clinical diagnosis of chloroma.

Pathological Diagnosis. Primary carcinoma of pancreas; metastases in vertebræ, retroperitoneal glands, mesentery, adrenals, testes, and bronchial nodes. Syphilis of testes.

30. CASE MRS. B.—Age (?). No history or symptoms of syphilis. Wassermann negative on blood, 4+ positive on spinal fluid. Eight months pregnant. Clinical diagnosis of tuberculous meningitis. Miscarriage. Dead fetus.

Pathological Diagnosis. Lobar pneumonia. Chronic tuberculosis of bronchial nodes. Miliary tuberculosis of lungs, liver, spleen, and peritoneum. Caseation of one adrenal. Syphilis of myocardium and of fetal chorion.

31. CASE B.—Age, forty-two years. Gonorrhea at twenty years of age. Denied syphilis. Wassermann negative. Drinker. Clinical diagnosis of alcoholic cirrhosis.

Pathological Diagnosis. Alcoholic cirrhosis. Syphilis of heart, aorta, and testes.

32. CASE W.—Age, seventy-eight years. No history of syphilis. Wassermann positive. No clinical diagnosis.

Pathological Diagnosis. Syphilis of heart, aorta, pancreas, and testes. Syphilitic peribronchitis. Chronic parenchymatous nephritis. General marasmus.

33. CASE B.—Age, forty-eight years. No history of venereal diseases. Wassermann negative. Clinical diagnosis of prostatic enlargement and uremia.

Pathological Diagnosis. Primary carcinoma of prostate. Metastases in liver. Chronic cystitis, ureteritis, and pyelonephritis. Syphilis of heart, aorta, and testes. Fatty liver and adrenals. Pulmonary edema. General atrophy. Emphysema. Infected cystotomy wound.

34. CASE A.—Age (?). No history of syphilis. No Wassermann. Clinical diagnosis of diabetes. Mitral insufficiency.

Pathological Diagnosis. Diabetes. Atrophy of pancreas. Dilatation of heart. Purulent bronchopneumonia. Subacute parenchymatous nephritis. Syphilitic orchitis.

35. CASE AR.—Age, forty-eight years. No history of syphilis. Wassermann negative. Diagnosis of diabetes. Sepsis.

Pathological Diagnosis. Diabetes. Infected squamous-cell carcinoma of finger. Ascending purulent lymphangitis of right arm. Septicemia. Syphilis of heart, aorta, pancreas, and testes.

36. CASE AL.—Age, sixty-nine years. Denied venereal disease. Wife had one miscarriage. Drinker. Wassermann not taken. Diagnosis of croupous pneumonia and pernicious anemia.

Pathological Diagnosis. Croupous pneumonia. Syphilis of heart, aorta, and testes. Syphilitic contracted kidney. Anemia gravis. General atrophy.

37. CASE MRS. BO.—Age, forty-four years. No history of syphilis. Never pregnant; no precautions taken. Wassermann negative. Died of general peritonitis.

Pathological Diagnosis. Acute purulent peritonitis. Infected laparotomy wound, posthysterectomy. Syphilis of heart and adrenals.

38. CASE W.—Age, fifty-five years. Denies venereal disease. Moderate drinker. One Wassermann test negative, second one positive. Diagnosis of alcoholic cirrhosis.

Pathological Diagnosis. Alcoholic cirrhosis. Ascites. Portal stasis. Syphilis of heart, aorta, and testes. Emphysema. Chronic prostatitis.

39. CASE J.—Age, seventy-two years. Denies venereal disease. Moderate drinker. Wassermann negative. Clinical diagnosis of myocardial insufficiency.

Pathological Diagnosis. Aortic insufficiency and stenosis. Sclerosis of endocardium. Mitral stenosis and insufficiency. Cardiac hypertrophy and dilatation. Syphilis of heart, aorta, pancreas, and testes. Syphilitic ulcer of leg. Emphysema. Brown induration of lung with multiple infarcts. Early interstitial nephritis. Early stage of alcoholic cirrhosis. General atrophy.

40. CASE C.—Age, fifty-nine years. Denied venereal disease. No Wassermann. Clinical diagnosis arthritis deformans of spine. Terminal pneumonia. Pyelonephritis.

Pathological Diagnosis. Primary scirrhous adenocarcinoma of prostate with metastases in vertebræ, ribs, pelvic bones, lungs, liver, and retroperitoneal lymph nodes. Aspiration purulent bronchopneumonia with abscesses of lung. Multiple abscesses in kidneys. Chronic cystitis. Syphilis of heart, aorta, adrenals, and testes.

41. CASE CA.—Age, forty-five years. Denied venereal disease. One Wassermann test negative; second one positive.

Pathological Diagnosis. Croupous pneumonia. Chronic ulcerative colitis with multiple polyp formation. Chronic dysentery. Amyloid spleen. Syphilis of heart.

It will be seen from the above list that there are 11 cases with clinical diagnosis of recognized and treated syphilis regarded clinically as cured, 5 cases of active syphilis under treatment for symptoms of the disease, and 25 cases in which a diagnosis of syphilitic infection was excluded clinically because of absence of symptoms and denial of previous infection. It is very probable that some, if not the majority, of the patients in this third group were actually in total ignorance of any specific infection. In the case of the women it is practically certain that this was the case. There can be no doubt that many people acquire syphilis without recognizing any of the earlier stages, either through ignorance of these or because the early symptoms are slight or entirely absent. Some of the male patients in this group no doubt had had the primary sore so long before that they had either forgotten it or no longer attached any importance to it. Having long ago accepted that condition as cured, they consider it as past history and deny that it ever took place. It is, of course, a very common experience in dealing with patients of this type to receive repeated denials of the occurrence of syphilitic infection, and the information of such an infection must be drawn out by special and prolonged tactics of questioning. It is also possible that a number of these cases were congenital infections, and unrecognized by the patients. Particularly in the case of women may congenital syphilis run an unrecognized latent course throughout the patient's lifetime.

In all of these 41 patients the lesions of active syphilis were practically of the same nature, whether in cases that had been treated, or were being actively treated, or had received no treatment at all. Active syphilitic lesions were found in the heart in 36 cases, in the aorta in 32, in the testes in 31, in the liver in 4, in the adrenals in 6, in the spleen in 1 case, pancreas in 6 cases, and central nervous system in 5 cases. As five of the patients were women, and deducting these, the lesions in the testes occur as frequently as those in the heart. The organs most frequently the seat of active lesions in order of frequency of occurrence would be aorta, heart, testes, adrenals, pancreas, central nervous system, liver, and spleen. It is also of great interest to note that in these cases there were 16 cases of subacute or chronic parenchymatous nephritis; 2 of acute parenchymatous and 5 cases of interstitial nephritis, although no relationship between the syphilis and the kidney lesions can be positively affirmed. It is very probable that the central nervous system would show a much greater rate of involvement had this been regularly examined, but in the majority of these cases an examination of cord and brain was not permitted. In all five of the active cases of Class II the central nervous system was examined and showed marked syphilitic lesions.

In the determination of the existence of syphilitic infection in any given case coming to autopsy the heart, aorta, and testis in the male are the organs that should receive the most thorough examination. If the latent syphilis is present, active lesions will be found in one or the other of these organs if they occur anywhere within the body. The triad of interstitial myocarditis, aortitis, and orchitis fibrosa may be taken as a pathological complex indicating the occurrence of a syphilitic infection in the male. In medicolegal work these three organs should be chosen in preference to all others for microscopic examination when the question of syphilis is concerned. In the case of the female, the heart and aorta, pancreas and adrenals should be examined for evidences of latent syphilis, and the lesions in these organs are, as a rule, less marked than in the male body.

The number of spirochetes in old latent syphilis is usually small; only in a few cases have they been found in numbers at all approaching those of early congenital or acquired syphilis. They lie in small groups or colonies in small perivascular infiltrations; usually outside of the walls of small veins. This is particularly true in the case of the aorta, where the organisms are never found in the intimal side of the vessel, but are found colonized in the outer portion of the media, or, most frequently of all, in the adventitia around the veins of the vasa vasorum. In the heart muscle they are found in small areas of connective-tissue proliferation and infiltration around the smallest branches of the coronary vessels, particularly the veins, and in similar areas in the muscle. The amount of inflammatory infiltration may be very slight. The pancreas in every case of latent syphilis shows more or less pronounced increase of stroma, areas of intralobular pancreatitis, atrophy, and perivascular infiltrations. The syphilitic nature of all these changes has not yet been determined. Only in one of the diabetic cases have spirochetes been demonstrated in the pancreatic lesions. It is of interest to state here that six autopsy cases of diabetes occurring in our service since 1907 have all shown histological changes of syphilis, and in four of these cases spirochetes have been demonstrated in the myocardium. The adrenal lesions consist of mononuclear infiltrations in the medullary portion or at the boundary between cortex and medulla, around the veins, and also thickening of the corpuscle. Spirochetes have been demonstrated in the infiltrated areas. The lesions of the testes consist of vacuolation and disappearance of the germinal cells, hyaline thickening of the basement membrane of the tubules with gradual obliteration of the seminiferous tubules, the so-called orchitis fibrosa syphilitica chronica. A state of fibroblastic proliferation precedes the hyaline change, and spirochetes are found in the basement membrane in this early state. Small collections of mononuclear cells may be found between the tubules in the neighborhood of small vessels. Spirochetes may be found in these areas also. The close relationship of the spirochete to the seminiferous tubules makes the entrance of the organism into the tubule a very probable occurrence, and can be taken as a very strong argument for the possibility of seminal infection. In congenital syphilis and in early acquired syphilis I have found the testes swarming with spirochetes even when no histological changes can be recognized in the organ. In such cases great numbers of spirochetes must gain entrance to the tubules and pass out with the semen. The difficulties in proving this are, of course, very obvious.

I have taken as a criterion for diagnosis only morphologically typical spirochetes, and have based my findings only upon the demonstration of those showing characteristic quality and morphology. In addition to typical organisms, we find in the old latent cases especially irregular and atypical forms (beaded forms, straight forms, fragmented forms, thicker or thinner spirals, etc.) in the colonies with the typical forms. I believe these to be involution forms, but am not yet prepared to make positive statements concerning this point. This point is now being investigated. The beaded and fragmented forms may in part be postmortem changes, since they can be produced in spirochetes in syphilitic tissues left in the cold or warm room for some hours after removal from the body before the formol-fixation. Experiments with liver, spleen, and lungs of congenital syphilis containing innumerable spirochetes show that similar changes in the spirochetes can be produced by the conditions mentioned above. Taking the typical spirochetes as our criterion, there can be no question of any confusion with fibrillæ of reticulum, elastic tissue, etc. The latter, even when heavily precipitated with silver, never resemble the spirochete in morphology or quality to such an extent as to make confusion of identity possible.

Our autopsy material comes almost wholly from the University Hospital, a State hospital whose patients represent the average middle-class population of the State. It is important to note the prominent incidence of latent syphilis in this class, about one-third of the adult autopsies. Still more important is the fact, already mentioned, that the greater part of these latent cases give no clinical history of syphilis, and are in ignorance that they have acquired the disease. They entered the hospital for other conditions, most prominent of which are cardiovascular-renal symptoms and conditions. Only the autopsy reveals that they are spirochete carriers and have a latent infection of very low virulence, which in all of the cases must be very old, and not recent, because of the fibroid character of the lesions. Most of the lesions found represent healed syphilitic areas; but in all cases active areas of inflammation are still present, and can always be found after a search more or less prolonged, as the case may be. The same histological changes, often of the same degree and extent, occur in the heart, aorta, pancreas, and testes of all cases of syphilis, treated, "cured," untreated, and unsuspected.

The sociological importance of this is very great. It places latent syphilis upon a plane of importance nearly, if not equalling, that of tuberculosis, as a factor opposed to the health and progress of the race. Latent syphilis, I believe, will be found to be the chief factor in the production of myocardial insufficiency and the cardiovascular-renal complex, apparently so rapidly increasing.

My pathological experience makes me believe that the heart and aorta of every latent syphilitic are involved in the infection. From the stand-point of life insurance, latent syphilis becomes a medical and sociological factor of the greatest importance. The spirochete carrier is a bad risk. He is also a possible source of danger through infection to those with whom he lives in most intimate contact. In these old latent cases seminal transmission is probably the most dangerous possibility to be considered.

The question of a possible reinfection has been suggested in explanation of some of these cases. No clinical evidence, of a second infection, of course, exists in any one of these cases; and in most there is no history of the first infection. I think such a possibility very improbable. I, myself, have never seen a true reinfection, and regard the relatively few cases described in the literature as not above suspicion. Sores in all respects resembling the hard chancre may appear upon the genitals or other portions of the body in late active and treated cases of syphilis. Even on microscopic examination they cannot be distinguished from the primary chancre. A primary sore may also be made to disappear early by the use of preventive or curative mercurial ointments or by one or two injections of salvarsan; but it may return after a few weeks or months. I have seen several cases in which such a recurrence of the chancre took place six months after the primary sore had disappeared under such treatment, and without chance for reinfection. In one case recurrence took place one year later. Had opportunities for reinfection been present, such recurrent primaries might easily be regarded wrongly as reinfections.

I believe that many of these latent cases without history are innocent congenital cases or are the victims of familial infection. Congenital syphilis, in the female, and in the third generation has an especial tendency to run a mild latent course, sometimes without any clinical sign or symptom. It may not be recognizable at all during life. The same thing is sometimes true of certain familial infections; certain members of the infected family may show absolutely no clinical signs or symptoms, except perhaps a positive Wassermann. This may also be negative. In other cases obscure signs of the disease (ocular alone) may be the only evidence found of the infection. The sociological and medical problems associated with congenital syphilis are very great, and we are just beginning to appreciate them.

As to the Wassermann reaction in latent syphilis a certain percentage of cases will give a positive reaction, but many will be found to have a negative reaction. Blood and spinal fluid will often give contradictory results. Under given conditions only strongly positive reactions have any positive diagnostic value; the negative Wassermann cannot be taken as any evidence of the absence of latent syphilis.

The apparent symbiosis of spirochetes within such organs as the heart, aorta, and testes through a period of many years without causing greater damage or giving rise to more marked symptoms must be taken as proof that the organisms have a very low virulence in such cases. "Cured" syphilis in many cases, if not all, is but a latent infection or "symbiosis," with spirochetes that have a very low virulence, in some cases not much greater than that of the intestinal flora. It becomes increasingly important to know the conditions under which organisms remaining so relatively inactive over long periods of time may at times renew their aggressiveness and cause more marked damage.

The general hygiene of the spirochete carrier is probably of as great importance as the general hygiene of latent tuberculosis. This is a point not yet sufficiently emphasized in the treatment of syphilis.

The therapeutic lesson is evident. Promises of cure within definite time-limits can never be safely made, and our advice as to treatment must include the possibility of treatment extended over many years. The syphilitic must be treated as a germ carrier. The latency of the infection seems to be the same in many untreated cases as in those receiving very good treatment. Our present-day treatment seems only to succeed in rendering the infection latent rather than in curing it. Clinical cures may not be cures at all, as shown by the autopsy. From the stand-point of eugenics it may also be said that absence of symptoms, or even of history of infection, and negative Wassermann reaction cannot be taken as an absolute criterion of freedom from latent syphilis.

HEREDITARY SYPHILIS IN THE LIGHT OF RECENT CLINICAL STUDIES.[1]

By Borden S. Veeder, M.D.,
ST. LOUIS, MISSOURI.

(From the Department of Pediatrics, Washington University Medical School, and the St. Louis Children's Hospital.)

Transmission. Whatever may have been the real position of Paracelsus—whether a great physician out of touch with his times or a master quack—we must credit him with being the first to assert the existence of an inherited form of syphilis. This was in the year 1529, a short time after the introduction of the disease into Europe from the West Indies; but a general belief in the transmission of syphilis from parents to offspring did not prevail until the latter part of the seventeenth and eighteenth centuries, although an infantile form of syphilis was well recognized. With the acceptance of the general idea there has been a century-long controversy in regard to the details of the method of transmission, which, expressed in its simplest form, has centered about the question of whether or not syphilis in the father can be transmitted to the child *in utero* without the mother at the same time becoming infected.

Without going into the historical details of the years of controversy, we can briefly sum up the position taken by the two most prominent groups of syphilographers. One group has held to the view of germinal transmission, which to a large extent is based upon the observations that:

1. In most cases of inherited syphilis the father is admittedly syphilitic.
2. That many women without clinical signs or history of lues bear syphilitic children to a syphilitic father.
3. That the treatment of a syphilitic father in many instances has lead to the mother bearing normal children after having previously given birth to a syphilitic child.
4. That instances are known of where an untreated woman has borne syphilitic children to a syphilitic father and subsequently normal children to a normal father.

The last two observations do not always hold true and the question at issue really involves the second observation—that is, of healthy mothers giving birth to syphilitic children. It is admitted that in many cases the mother is syphilitic, being anteconceptionally, conceptionally, or postconceptionally infected.

In 1837 Colles published the observation that apparently normal women bearing syphilitic children acquire an immunity to syphilis, or, more correctly, do not contract syphilis when exposed to infection. This has been interpreted in two ways: (1) as an expression of a passive immunity due to the absorption of immune bodies from the syphilitic fetus through the placenta, and (2) as the result of an active immunity, the woman having syphilis. According to the ideas of those who believe that in all cases the mother is infected, it is only the negative Colles' mothers—that is, the few reported cases in which the mothers of syphilitic children have subsequently become infected with syphilis—which lend any valid support to the theory of the possibility of a purely paternal infection, and the accuracy and correctness of the clinical observation has been questioned in these cases. The second group, as we have said in discussing the first, holds to the view that the mother is always infected, and that without maternal syphilis there is no syphilis of the offspring.

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[1] Read before the Kansas City Academy of Medicine, January 7, 1916.

This controversy, which lasted for so many years, was based upon the interpretation of clinical observation, and in brief depends upon whether or not germinal infection is possible—that is, whether the spermatozoön can carry the infection and the offspring become syphilitic without the mother acquiring the disease. Within the last decade—for it was in 1906 that Schaudinn's first paper appeared—our knowledge of syphilis has increased more than in the entire period of time elapsing since its recognition in the latter part of the fifteenth century, and the discovery of the etiological organism and of serodiagnostic methods have helped to clarify in many ways the questions which have confused this subject of inherited transmission.

The Treponema pallida of Schaudinn is an organism some 6 to 15 microns in length and with some 10 to 26 undulations. The head of a spermatozoön—which is the only portion capable of carrying an organism within it—is from 3 to 5 microns in length. Hence, the physical impossibility of the treponema being carried in the spermatozoön, which is essential if we are to have a true germinal transmission, unless the organism undergoes some morphological change in its life history with which we are at present unfamiliar and have no reason to suspect. Moreover, we know of no example of germ-cell transmission of an infectious disease in human or veterinary pathology. With everything thus against the possibility of such a method of transmission the burden of proof is with those who advance the theory, and as yet no evidence has been submitted in support of their position.

Although, in all probability, germinal transmission does not occur, as we have seen, it has been found that the seminal fluid can carry the infection, and the testicles are recognized as a not infrequent seat of latent syphilis. Finger was able to transmit an infection to two of the higher apes with seminal fluid from florid lues, and Neisser has transmitted the infection by transplanting the testicles of syphilitic apes. It has not been possible to demonstrate the presence of spirochetes in seminal fluid by microscopic methods. These experiments, it must be kept in mind, only prove the infectiousness of seminal fluid from active syphilitics, and do not bear a direct relation to the question of paternal transmission in hereditary syphilis.

Turning now to the question of women bearing syphilitic children who show no signs of syphilis: There are two possibilities—either the women are not syphilitic, or else they have syphilis in an inactive or latent form. With the development of serological methods for the diagnosis of syphilis, their applicability to this question was at once recognized and many small series of tests were soon reported. In these small series the percentage of positive reactions in the blood of mothers of syphilitic children ran from 40 to 60.

In a recent study of familial syphilis made in our clinic in St. Louis we had occasion to test the blood of 85 mothers of syphilitic children. Of these 85 mothers, 74, or 87 per cent., denied all knowledge of infection, nor was there anything in the history given us that would indicate a syphilitic infection outside of a history of frequent abortions. Dr. Jeans[2] has recently collected these cases and found that the blood of 73 of the 85 gave a positive Wassermann test. Of the remaining 6 all but one were tested after an interval of at least ten years had elapsed between the birth of the last syphilitic child and the time of the test. In the one exception the interval had been four years. In some of these cases a healthy child had been born during this period.

In this way, by means of the complement-deviation test, it has been found presumable that these apparently healthy mothers are immune, in Colles' sense, because they have syphilis in a latent form. Hochsinger, in order to uphold his older ideas, would have us believe that in these cases the positive reaction was an indication of immunity rather than of infection. This interpretation is incorrect, as a positive Wassermann indicates tissue response against superinfection due to the presence of the spirochetes rather than a true reaction of immunity. As long as the reaction remains positive a superinfection never occurs, but it is well known that when treatment has been pushed to a point where it has become persistently negative, a second "primary" infection has occurred in many cases. Thus we do not have an immunity in syphilis in the true sense of the term, and a positive Wassermann signifies infection. Hence, we must regard it as evidence of or a symptom of syphilis whether the infection is active or latent, as in the cases under discussion.

In the present state of our knowledge we can summarize the evidence as pointing to the view that in hereditary syphilis the mother is always infected, although very frequently the infection is latent and that true germinal infection does not occur.

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[2] Familial Syphilis, Am. Jour. Dis. Child., 1916, xi, 11.

Syphilis as a Social Problem. No accurate figures are available as to the incidence of hereditary syphilis. The disease is not reportable, and even if it were it is doubtful if the records obtained in this way would be of any value, as the condition is frequently overlooked, and when recognized would be concealed in many cases because of the stigmata attached. With improved methods of diagnosis we are beginning to learn that it is far more common than previously thought, as many conditions in which the etiology was obscure have been found to be the result of a syphilitic infection. Hospital statistics are of little value in this connection. In St. Louis we have been particularly interested in hereditary syphilis, and have admitted many cases to the Children's Hospital for study which would normally have been cared for in the out-patient clinic, and hence the proportion of syphilis to the total number of admissions is relatively high. We have seen between 300 and 350 children with an hereditary infection in three and a half years and have undoubtedly failed to recognize a number of cases. We have also found many cases of latent syphilis by testing the apparently healthy children of syphilitic families. What is more important is the number of obscure clinical conditions which have been found to be syphilitic in origin.

The importance and cost of syphilis to the family and the community is not generally appreciated. About this point we have collected some interesting information: For a period of about a year an attempt was made to obtain extensive data in regard to the family of every syphilitic child coming to the clinic, to examine all of the other living children as well as the parents, and to test the blood of each member by the complement-deviation method. In this way data was assembled for 100 syphilitic families. Many marriages (10 to 30 per cent.) remain sterile as a result of syphilis and others (13 per cent. according to Haskell) result only in abortions. Our material includes only those families in which a living child came under our direct observation and care.

In these 100 syphilitic families 331 pregnancies occurred which resulted as follows:

Abortions	100 or 30.2	per cent.
Stillbirths	31 or 9.3	"
Living births	200 or 60.5	"

Thus 40 per cent. of the pregnancies terminated in the death of the fetus before term. If the parents had been healthy and of the same social strata we might have expected 30 to 35 deaths before term, or a mortality of 10 per cent. instead of 40 per cent.

Considering next the 200 living births: At the time the data were collected 39 were dead and 161 alive, but 12 of the 161 died during the course of the investigation. Of the 161 examined 107 had both clinical signs of syphilis and a positive Wassermann; 5 were clinically positive but gave negative tests (in all of these the family gave a history of syphilis); 16, although negative as regards clinical manifestations, gave positive reactions, and therefore belong to the group of latent syphilitics. Thus but 33 of the 161 living children were free from the infection, and if we attribute the deaths occurring before term to syphilis, we find that of the 331 pregnancies in 100 syphilitic families but 10 per cent. escaped the infection. The toll is summarized in the following table:

331 PREGNANCIES IN 100 SYPHILITIC FAMILIES.

131 or 40 per cent. died before term 51 or 15 per cent. died after birth	55 per cent. dead
116 or 35 per cent. living but syphilitic	35 per cent. syphilitic
33 or 10 per cent. living and free from syphilis	10 per cent. escaped
331	

If we add to this record and take into consideration the physical condition of the parents—both of whom were syphilitic in almost all of our cases—we begin to grasp the appalling importance of syphilis from a social standpoint.

In order to show this in another way, studies[3] were made in our clinic in which the waste (total deaths to total pregnancies) occurring in 100 families in which we were treating children with contagious disease, and in 100 families selected at random from our records, were contrasted with the waste in 100 syphilitic families. These groups are designated as C. R. and S. respectively and the data briefly summarized in the following table:

Group.	Total pregnancies.	Deaths before birth.	Born living now dead.	Total.	Per cent. waste.
C.	444	46	70	116	26
R.	442	42	59	101	22
S.	453	116	104	220	48

The increase in the waste for the syphilitic group of 100 per cent. does not represent the total waste, as it is fair to assume that three-quarters of the living children are syphilitic and many of these defective.

There are many things of interest in connection with the question of family syphilis—the way in which the infection seems to die out, the apparent tendency to involvement of the nervous system in some families, for example, which cannot be discussed in the limits of this paper. The question of the transmission to the third generation, about which so much has been written by Fournier, requires mention in passing. In the light of recent discoveries this entire chapter must be rewritten, as definite tests can now be applied when before we had to rely upon clinical observation which was questionable in many of the cases quoted as examples of this form of transmission. Today, in order to prove existence of an infection being transmitted to the third generation, we must not only have a positive Wassermann test in the child, its mother, and its maternal grandmother, but also in the brothers and sisters of the mother. This is essential to exclude faulty observation, and cases fulfilling these conditions must be adduced before we can state definitely that transmission to a third generation occurs. We have no cases fulfilling these conditions in our records, although in some cases there is a strong clinical suggestion of such a mode of transmission. We recently had in the hospital the child of a mother with inherited syphilis. The child was mentally and physically defective, but was free from a true specific infection. This is probably the form in which hereditary syphilis shows itself most frequently in the third generation, but these children are not syphilitic in the sense of true inherited transmission.

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[3] Jeans and Butler, Hereditary Syphilis as a Social Problem, Am. Jour. Dis. Child., 1914, viii, 327.

Clinical Manifestations. Passing now to a consideration of some points in regard to the clinical manifestations of hereditary syphilis.

From a clinical standpoint we have found it of service to divide our cases of inherited syphilis into four groups:

1. Fetal.
2. Infantile.
3. Late or tardy.
4. Latent.

In the first group, under the term fetal syphilis, we include the cases in which manifest signs of lues develop *in utero*. Thus, stillborn as well as living infants are included. It is this form of syphilis which the obstetrician sees in his practice and the death rate is extremely high for the infants born alive. In the second group, infantile hereditary syphilis, are placed the cases which develop clinical lesions after birth and during the first year of life, and in the third group, "late" syphilis, those cases developing symptoms after the first year regardless of whether or not there have been previous symptoms during infancy. The last (fourth) group is made up of apparently normal children whose blood gives a positive Wassermann reaction. This group, as a rule, goes unrecognized unless some other member of the family shows clinical signs of syphilis and thus furnishes a reason for a blood test being made. That these cases are not uncommon is shown by the number of children developing "tardy" lesions with a negative history as regards clinical manifestations during infancy. While the "infantile" lesions have doubtlessly been overlooked in some of these patients with "late" lesions, this can hardly be the case with all. In the series reported above there were 16 latent cases among the 116 living syphilitic children in the 100 families.

One of the most striking things about the clinical manifestations of hereditary syphilis is the distinctive and almost uniform character which the lesions show in the infantile group and the varied and bizarre ways in which the syphilitic infection appears in the late cases. This has been compared with the secondary and tertiary manifestations of acquired syphilis, and in general the comparison is good, although not strictly accurate. There is no distinctive primary lesion in inherited syphilis in the sense the term is used in the acquired form, as the infection takes place through the blood. As will be shown below there is a certain period of latency or incubation time between the time the infection takes place *in utero* and the development of visible symptoms after birth, which in a way corresponds to the time elapsing between the appearance of the chancre and the secondary lesions in acquired syphilis. There is no satisfactory explanation of why syphilis develops in such diverse ways. It would seem probable that whether fetal or infantile syphilis develops in a given case depends upon the time infection takes place *in utero*, infection early in pregnancy leading to early death and abortion, and infection occurring late to the infantile cases. Between these two may be innumerable gradations.

As the infantile and tardy groups are the most important I wish to discuss these in more detail. I have recently, together with Dr. Jeans,[4] studied the records of 100 consecutive cases of the infantile type, and, unless otherwise stated, the figures given below refer to this series. Where the totals are under 100 for any given point it means that the data regarding the point under consideration were unsatisfactory in the number of cases omitted.

As a rule, the first clinical symptoms of the infantile group develop in the first two months of life (81 per cent.), and the majority of these in the first month. In the accompanying table the time of development of the earliest symptom is shown for 95 cases:

Time of appearance.	Cutaneous eruptions.	Rhinitis.	Epiphysitis.	Wasting and Wassermann.	Jaundice.	Hemorrhage and edema.	Total.	
1 week	4	12	..	..	..	.....	16	Total in first month, 51
2 weeks	2	3	..	..	..	.....	5	
3 weeks	3	6	5	..	..	.....	14	
4 weeks	7	6	2	..	..	1	16	
5 weeks	..	1	1	..	..	.....	2	Total in second month, 30
6 weeks	6	7	..	..	..	.....	13	
7 weeks	2	3	..	..	..	.....	5	
8 weeks	6	1	1	1	1	.....	10	
3 months	5	1	..	..	..	.....	6	
4 months	1	1	..	3	..	Iritis 1	6	
6 months	1	..	..	..	..	.....	1	
10 months	1	..	..	..	..	.....	1	
Total	38	41	9	4	1	2	95	

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[4] Observations on Infantile Syphilis, Am. Jour. Dis. Child., 1916, xi, 177.

In the majority of the infants developing lesions early a rhinitis or coryza was first noted, but in the entire group the number of cases in which a rash was noted first is about the same. The most striking thing about these cases is that so many do not develop lesions until so long after birth, although infection takes place *in utero.* Two explanations are possible: one is that the infection varies both quantitatively and qualitatively in different cases—that is in one few organisms and in another many may gain entrance—or that the organisms may vary considerably in their virulence. With these variables any number of gradations are possible. A very plausible explanation, suggested by Rietschel, is that in these infantile cases the fetus is not infected until near the end of the pregnancy, when the beginning uterine contractions, which may precede parturition by a number of days, open a portal of entrance for infection by breaking loose the placental villæ and tearing open the sinuses, in this way opening a direct route for the transmission of the spirochetes. After a more or less definite period of time clinical signs of the infection appear, and the length of this time after parturition is dependent upon the time previous to parturition at which infection takes place. There are a number of obvious objections to this being more than a partial explanation.

It is a common statement that syphilis in an infant shows itself in two ways: either by producing a general dystrophic condition or by the appearance of more or less specific lesions. As a matter of fact, the two are usually combined and the first occurs but rarely as an entity. It was formerly supposed that many of the various congenital malformations had a luetic basis, but it has been shown by the Wassermann test that there is no relationship between the two more than that of a chance association. Thus, Holt[5] did not find a single syphilitic infection among 56 consecutive infants with congenital malformations (spina bifida, congenital heart disease, hare-lip, etc.), and in our experience it is not a common occurrence, although we have found the two occasionally associated. On the other hand, Browning[6] obtained 17 positive reactions in 20 patients with congenital heart disease, and Findlay,[7] of Glasgow, in 7 of 11 patients. In the parents of 2 of the 4 negatively reacting cases the reaction was positive. Naturally, I am inclined to trust our own experience and doubt very much if there is any etiological relationship between inherited syphilis and congenital malformations.

As intimated above the specific infection exerts a harmful influence upon the nutrition of the infant much greater than that which accompanies any type of chronic or acute infection, and this, no doubt, is the result of the widespread distribution of pathological lesions throughout all of the viscera. To show the extent of this malnutrition we compared the weights of 77 syphilitic infants at the time of the first examination with the average weights of a like number of normal infants of the same ages: 7 were overweight, 10 of average weight, and 60 below average weight. The entire group of 77 cases averaged 1480 gms., or a little more than 3 pounds below weight. This wasting, or malnutrition, is of extreme importance, as the outcome of any individual case depends more upon the state of the infant's nutrition than upon the specific treatment.

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[5] Wassermann Reaction in Hereditary Syphilis, etc., Am. Jour. Dis. Child., 1913, vi, 166.

[6] Syphilis and the Health of the Community, British Med. Jour., 1914, i, 77.

[7] Hereditary Syphilis, Glasgow Med. Jour., 1914, lxxxii, 401.

Associated with this wasting the large part of the cases of infantile syphilis show one or more of three symptoms: a rash, a rhinitis or coryza, and a palpable spleen. The first was present in 77 per cent., the second in 74 per cent., and the third in 82 per cent. of the 100 cases in our series. These might be called classical symptoms and require no discussion, but in passing I might add that in our series a desquamative dermatitis, particularly of the palms of the hands and the soles of the feet, was far more common than a macular or maculopapular eruption. This is contrary to the teaching in most text-books.

Epiphysitis is a common lesion and can be demonstrated in many of the stillborn infants by incision through the lower end of the femur, or by a line of enlarged calcification seen in roentgenographs of long bones in infants with syphilis. In these cases nothing is visible clinically until the process extends to the tissues surrounding the bone and the muscles become involved. This produces "Parrot's pseudoparalysis," which is erroneously termed epiphysitis. This external involvement was present in 14 of the 100 cases in our series. A condition frequently overlooked is an iritis or choroiditis in early infancy. Everyone is familiar with the keratitis of "late" syphilis, but eye examinations, and particularly ophthalmoscopic examinations, of young infants are so infrequent that these ocular manifestations which we find quite frequently are missed in many cases.

Perhaps the question of greatest interest in connection with these syphilitic infants is their outcome or future; 40 per cent. of the infants in our series died in the first year of life, and this despite the fact that most of them received intensive treatment. Other observers report a similar or higher mortality, and I have not run across any lower figures. Among those who do not die a small number develop lesions which lead to permanent symptoms—cerebrospinal syphilis, etc.—and in the sense that these permanent changes are the result of syphilis may be said never to clear up. In about half of the cases the signs of the infection disappear, either as the result of treatment or seemingly from some inherent reason. Unfortunately these cases are, as a rule, lost from view.

In a certain percentage of children developing late lesions there is a history of infantile lesions, but it would seem that in some of these early cases the infection becomes latent or dies out. There are no statistics on record of how many infantile cases develop late lesions. Between the second and the fifth years relatively few patients with active signs of inherited syphilitic infection are seen, but from then on until puberty many cases are encountered. As stated before, but few of the late cases give a history of previous lesions and the infection seems to have been latent since birth in the majority. The factors which lead to the development of these acute cases in late childhood are unknown. We know that, as a general rule, any infection in childhood lowers a previously acquired immunity or resistance to some other infection, as the lowering of resistance to tuberculosis following measles, and it is probably in something of this nature that the explanation for the development of acute lesions in long-standing quiescent syphilis will be found. Trauma would seem to be a factor in some cases.

It is the growth in the past few years of the number of pathological conditions which have been shown to be the result of "tardy" syphilis that has made the study of inherited syphilis of so much importance and interest. In order to show the protean character the infection assumes in childhood, and how little related are the clinical conditions due to the same infection, I have tabulated the lesions occurring in 100 cases of late syphilis. These are made up of two series of consecutive cases, one of 74 reported one and a half years ago[8] and the last 26 cases admitted to the Children's Hospital.

BONES:	
Periostitis tibia	4
Periostitis skull	1
Osteomyelitis	1
JOINTS:	
Acute arthritis knee	8
Acute arthritis ankle	1
SKIN:	
Macular eruption	1
Condyloma anus	3
Gummata	3
Alopecia	3
EYE:	
Interstitial keratitis	24
Choroiditis	1
ULCERATIONS:	
Nasal	2
Laryngeal	1
Pharyngeal	1
CENTRAL NERVOUS SYSTEM:[9]	
Mental deficiency	23
Cerebrospinal syphilis	14
Hemiplegia	6
Epilepsy	5
Spastic paraplegia	4
Chorea	2
Hydrocephalus	2
MISCELLANEOUS CONDITIONS:	
Ozena	1
Enlarged spleen (only symptom)	1
Torticollis	1
Aortitis	1
Obscure abdominal pain	1
Obscure pain in legs	2
Endarteritis obliterans	1
Paroxysmal hemoglobinuria	1
Raynaud's disease	1
Hutchinson's teeth	4

The thing standing out most prominently in this table is the great preponderance of syphilis of the central nervous system.

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[8] Veeder and Jeans, Late Hereditary Syphilis, Am. Jour. Dis. Child., 1914, viii, 283.

[9] 47 patients showed lesions of the nervous system.

This is contrary to the usual teaching of hereditary syphilis. Holt, for example, in the last edition (1911) of his text-book says of hereditary syphilis, "The different lesions of the central nervous system which may be due to syphilis are all quite rare." In 47, or approximately one-half of our series of 100 "late" cases, the infection appeared in some form of lesion of this system. The other conditions, as periostitis, Hutchinson's teeth, arthritis, interstitial keratitis, etc., which are usually described as the most common, were all present in the series, but in a much smaller percentage.

I have gone over our records to find in what percentage some of these conditions have a syphilitic basis. Hydrocephalus has always been charged against a specific infection to a greater or less degree. Of 13 cases upon which we made Wassermann tests, 3, or about 23 per cent., were positive; 31 cases of epilepsy have been tested, and 6, or 20 per cent., gave positive reactions. Spastic paraplegia is most interesting, as only recently has there been a connection with syphilis suggested. Syphilis was present in 3 of 10 cases, or 30 per cent. in our records. Holt did not happen to meet with a single positive case in eight tested, but Findlay obtained 13 positive tests in a series of 33 cases examined. Hemiplegic children gave the highest percentage of positive reactions, 6 out of 12 cases, or 50 per cent., having syphilis.

A few years ago a French writer, whose name I have forgotten, reported that he had obtained positive reactions in nearly all of a small series of children with chorea. This was not confirmed by subsequent investigations, and it is probable that considerable error in the technic of making tests must have crept in. We have tested nearly 40 cases of chorea and in 2 obtained positive reactions. In 1 of these the chorea apparently had a syphilitic basis, but in the other it might have been a chance association. Neither had any signs of a rheumatic infection. The one case—a maniacal chorea—responded immediately to specific treatment. In order to see if the therapeutic test was of any value we treated several non-specific choreics in the same way without the slightest effect being produced. Comby[10] has recently reported that he found evidence of syphilis in 7 of 39 cases of chorea, but Koplik[11] in a smaller series came to the conclusion that there was no relationship between the two.

Mental deficiency has been a favorite subject of study from the standpoint of syphilis in the last few years, and with the most contradictory results when large groups of institutional defectives have been examined. What, from our view-point, is of more importance than the percentage of mental deficiency due to syphilis is the number of syphilitic children showing mental deficiency.

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[10] Etiology of Chorea, Arch. d. Med. d. Enf., 1915, xviii, 517.

[11] Relationship of Syphilis to Chorea of Sydenham, Arch. Pediat., 1915, xxxii, 561.

Thus 23 out of 100, or approximately one-fourth of the "late" group, were defectives. In addition then to the high death rate of inherited syphilis we must add one-quarter of the living children as "worse than dead."

Recently a new test for the presence of protein substances in the spinal fluid has been advanced which it is claimed is of value in the differential diagnosis of cerebrospinal syphilis from other diseases of the *central nervous* system. This is the "colloidal gold" or Lange test, in which various dilutions of the spinal fluid under investigation are added to the reagent in a series of tubes. According to the discoverer of the test each disease produces a color change in certain tubes—or a zone of color change—which is characteristic of the disease. Thus in syphilis the zone of change is in the lower dilutions and in tuberculous meningitis in the higher. As yet the test has been almost exclusively used in the diagnosis of paresis and other parasyphilitic conditions. Dr. Meredith Johnston has been making a general study of the spinal fluid in childhood in our laboratory, and among his cases were 20 of hereditary syphilis. All of these gave a positive Wassermann on the blood. In 15 of the 20 cases the central nervous system was involved. In 14 of these 15 the Lange test was positive while the Wassermann was only positive on the spinal fluids of 8 of 14 tested. Thus only 1 case gave a negative Lange while in 6 the Wassermann was negative. Both the Wassermann and Lange tests were negative on the spinal fluids of all 5 cases without clinical signs of central nervous involvement. The only other disease which Dr. Johnston has found which gives a similar zone of change to that occurring in cerebrospinal syphilis is acute anterior poliomyelitis, and in this the reaction is only transitory and not persistent as it is in syphilis.

WASSERMANN REACTIONS. From what has been said it is obvious that we attach a great deal of importance to the Wassermann reaction. Like all delicate laboratory tests it is only of value when carefully controlled and made by a skilled technician. A poor Wassermann test, or one in which there is a question as to the accuracy of the worker, is worse than none, while a good test is of great value. We look upon a Wassermann reaction as a symptom or an indication of infection rather than of immunity, and in this sense it is comparable with the tuberculin reaction. When a case of syphilis is cured the reaction becomes negative, but the patient again becomes susceptible to infection, and a number of cases have been reported where this has taken place. The longer the infection has been present the more apt is the reaction to be positive, hence the high percentage of positive reactions in tertiary and parasyphilis, and likewise in inherited syphilis. We have seen but one patient with late hereditary syphilis whose blood failed to give a positive reaction, and in this the diagnosis was somewhat questionable. For practical purposes then we can say that in our experience all of the cases of late hereditary syphilis give a positive reaction. This does not hold true for the cases of an infantile type. In the series of 100 cases reported above the blood was tested in 82 with the following result:

Positive	76 or 92.6	per cent.
Doubtful	1 or 1.3	" "
Negative	5 or 6.1	" "

For the two types (over 300 cases) the percentage of positive reactions is about 98. This corresponds with the figures of Boas,[12] who states in his book on the Wassermann reaction that hereditary syphilis gives a higher percentage of positive reactions than the other forms. He tested 53 infants with manifest lues and 54 older children with late lesions and all reacted positively. A number of newborn syphilitic infants reacted negatively, although most of this type of cases gave a positive reaction. A number of writers have called attention to the fact that a small percentage of newborn infants give a negative reaction and later a positive one. This may be explained on the basis that infection occurred just before birth and that some time must elapse before the formation of reactive bodies. Three of the five negatively reacting infantile cases in our series do not belong in this group, as two were three months of age and one five months when tested. All were clinically syphilitic and there was syphilis in the parents of the one child whose parents submitted to tests. Positive reactions in non-syphilitic children are rare, so rare I feel the technic must be faulty. I can recall having seen but one such case, and this reacted negatively on a control test. Lederman found 3 in 650 non-syphilitic infants, and these might have been latent cases. Occasionally a weakly positive transitory reaction has been reported in scarlet fever, pneumonia, influenza, and other infections. We have tested a number of scarlet fever cases as well as other febrile conditions without finding a single positive reaction.

We can say then that positive reactions in non-syphilitic patients are extremely rare, that in all of the patients with the late type and over 90 per cent. with the infantile type of hereditary syphilis the Wassermann reaction is positive. It is understood, of course, that these figures refer to untreated cases.

My personal experience with the luetin test of Noguchi is very limited. It most certainly cannot offer any advantages over the Wassermann reaction insofar as the furnishing of diagnostic information in hereditary syphilis is concerned, and as we have had dependable laboratory workers making tests we have neglected the luetin test. Its simplicity offers great practical advantages.

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[12] Die Wassermansche Reaktion (2d ed., Berlin), 1914, p. 119.

Recent reports have been somewhat more favorable than the early ones, but the opinion is quite general that the Wassermann reaction is the preferable of the two.

Treatment. In general we are accustomed to regard hereditary syphilis as a disease particularly amenable to treatment. If we judge the results of the treatment by its immediate effect upon clinical symptoms this holds true, but it is not true when we consider treatment in its relation to the ultimate cure of the disease. Most acute hereditary syphilitic lesions disappear rapidly under specific treatment with the exception of interstitial keratitis, but the chronic lesions of the central nervous system are but little affected. It is extremely difficult to obtain a persistently negative Wassermann reaction as the result of treatment, and particularly so in the "late" cases. We have treated some cases intensively and persistently for over three years without effect. We have obtained negative Wassermann reactions in the infantile cases following intensive treatment, but in surprisingly few cases considering the entire number treated. In these "infantile" cases, as a matter of fact, the outcome of the case, as far as life or death is concerned, depends far more on the condition of the patient's nutrition than upon the character of the specific medication. If a long series of cases are studied it will be found that the therarpeutic results are disappointing as a whole.

We have used various methods of treatment in our cases, including over 100 in which neosalvarsan was used in combination with mercury. It is the drug of choice to make an acute lesion—as a rash or an arthritis for example—disappear in the shortest time, but for the long-continued treatment which is necessary mercury is preferable. The most satisfactory form of mercury for use with children in our experience is gray powder.

REPORT OF A CASE ILLUSTRATING THE ANATOMICAL SEAT OF MOBILE SPASMS.

By Charles L. Dana, M.D.,

and

Belden Gere, M.D.,

CORNELL UNIVERSITY MEDICAL COLLEGE.

The following is the history of the case of a child who, from the age of six months to the sixth year when he died, suffered from continual choreic and tonic spasms, involving nearly all the muscles of his body, including the neck and face.

The case has this importance that it shows an anatomical seat of such spasms as those of chronic chorea, of spasmodic tics, and of myotonia.

SUMMARY. A child, aged six years, born prematurely; normal until the fourth month; then an attack of stupor, etc., diagnosed as "meningitis," then development of clonic and tonic movements involving face, throat, neck, trunk, arms, and legs, the legs being mainly rigid, so that the child could only imperfectly stand or walk; no paralyses, no atrophies, no anesthesias, special senses normal, intelligence retarded, but not seriously.

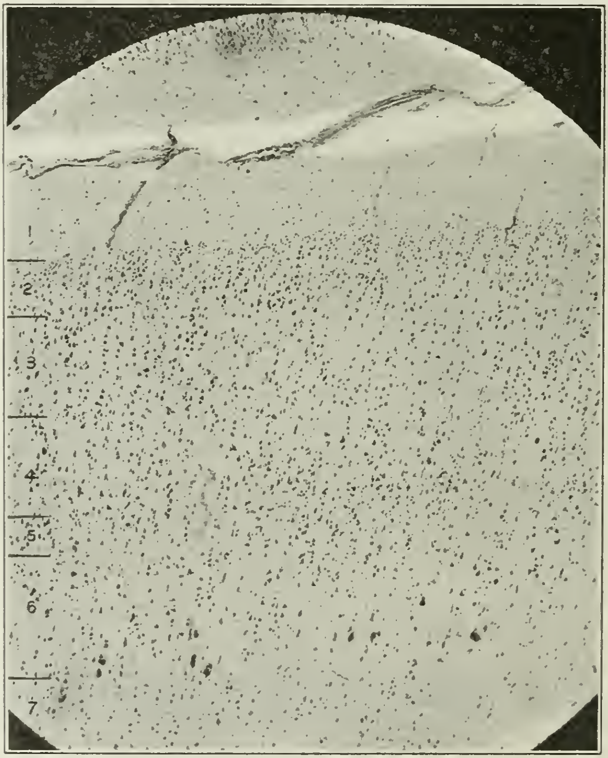

Fig. 1.—Anterior cerebral convolution; arm area × $\frac{2}{3}$. Compare Fig. 14. The lines on the side indicate approximately the cortical lamina of this area according to Campbell.

Duration of condition five and one-half years. Death following operation to resect posterior spinal roots.

Autopsy. No gross lesion of brain or cord; brain of normal size and weight.

Microscopically the motor and premotor cortex showed disturbance in lamination of cells, degenerative changes of cells, deficiency in size and number of large pyramidal cells. Changes less marked in posterior central convolution. Changes similar to those of ante-

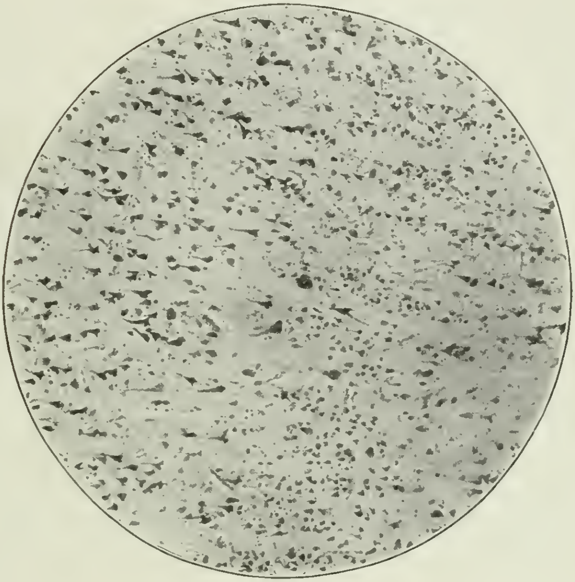

FIG. 2.—Anterior central convolution; arm area × $\frac{1}{130}$, showing fourth, fifth, and sixth layers.

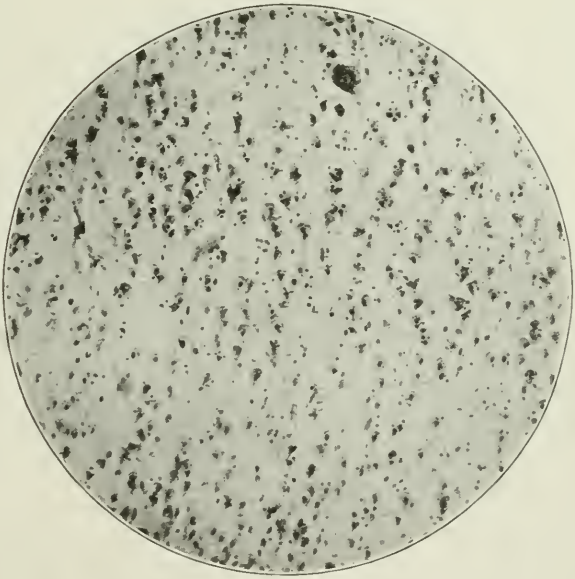

FIG. 3.—Anterior central convolution; arm area × 200.

rior central convolution though much less marked in the thalamic and subthalamic region. Nuclei of columns of Goll and one pyramidal tract show some deficiencies.

The tonic and clonic spasms with some permanent rigidity of the lower extremities were the main features of the case. The tonic spasms caused an apparent spastic paraplegia, although there was no real paralysis, nor objective evidence of involvement of the pyramidal tracts, and both the corticospinal and the peripheral motor neurons showed no or slight signs of degeneration.

History. K. R., male, aged three years and eleven months was brought to me for consultation by Dr. Morissy, of Connecticut. He is the second of three children. The parents are healthy with no history of lues. The boy was born prematurely (six weeks before the time) with a rather long labor, but without any instruments. He had no convulsions, and he grew like a normal child until he was about four months old, when he was taken with what was called "meningitis" and was ill in bed for several weeks. He had a number of convulsions at that time and was in a stuporous condition

After coming out of this he began to develop clonic and tonic spasmodic movements involving the face, tongue, neck, trunk, and extremities; these continued without interruption.

He was first seen by me in April, 1909, when he was three years and eleven months old. He was then fairly well grown but poorly nourished.

His body and extremities, neck and face were in continuous spasmodic movements. The legs were kept mostly in extension, but there was no permanent and absolute contracture and he could at times support himself and with much help could walk a little.

He could not hold up his head, sit up or stand alone, mainly because of the continuous spasms. The head and neck were particularly affected with clonic and tonic spasms of the right accessory which pulled it toward the left as in wry-neck. There were also retrocollic spasms which pulled his head backward; also spasms of the facial muscles and of the tongue, so that he spoke only indistinctly, though he could talk a little. He understood what was said to him, and though somewhat retarded, he seemed to be fairly intelligent. The eye muscles were not involved, the special senses of vision and hearing were normal.

The limbs were well developed and rather muscular, but were in a spastic condition much of the time. The arm movements were jerky and irregular, and he could not easily bring his hand to his mouth or perform any purposeful acts.

The deep reflexes were exaggerated, and there was a doubtful dorsal toe reflex, but no ankle clonus. There was no anesthesia, superficial or deep.

The boy had a normal sized head, but there was a slight bilateral depression in the skull over the motor area on each side. He had a narrow palate and shell ears.

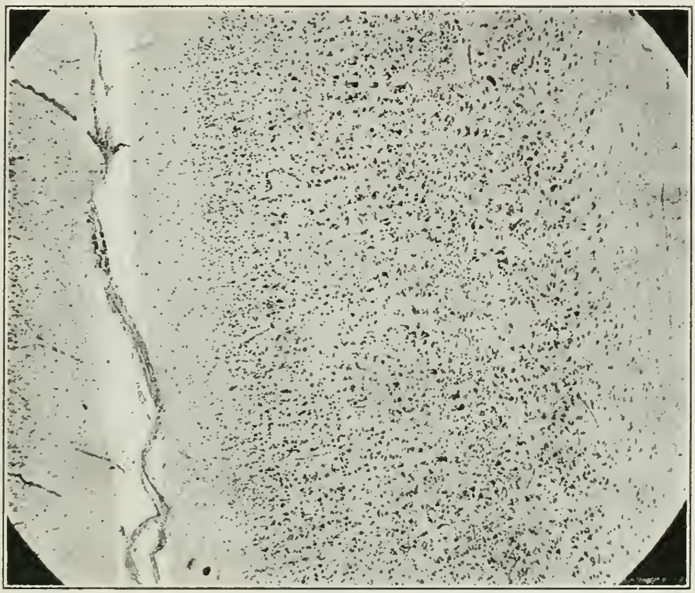

FIG. 4.—Posterior central convolution; arm area × $\frac{2}{3}$.

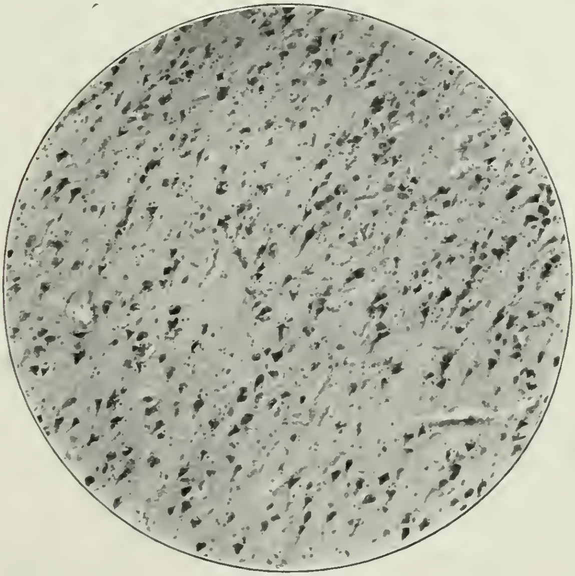

FIG. 5.—Posterior central convolution: arm area × 130.

Three years later the child was brought to me again and sent to the Neurological Institute (December 12, 1912). At that time the following notes were made upon him:

"Child pitifully undeveloped and under nourished. Is seen lying always with the head turned to the right, his arms flexed upon the elbows, his hands clenched, and these tossing and beating about his face and head. The arms can be straightened only with force and then resume their contractured position at once, unresisted.

"The trunk is more quiet than the head or arms and the legs do not move about like the arms, but are held extended partly with the knees slightly flexed. When the child is lifted and his feet brought to the floor he makes no attempt to support himself, and his head is drawn far backward upon the shoulders.

"At the sight of food when hungry the child's movements become greatly increased, the mouth opens widely on the left, the right side hardly sharing in the movement; the hands beat widely about the mouth as though some attempt were being made to assist himself. The feeding of the child is therefore difficult. It is best accomplished by two persons, one to hold him in the sitting position with the back and head supported and his arms clasped in a towel or blanket to prevent them from jerking into his face and mouth spasmodically, and the other person to bring the milk to his mouth in small quantities.

"He cries repeatedly for his mother (a sound similar to 'udda'), and when asked if it is his mother he means, he quickly answers 'ya.' When given a toy rooster in a cage and told what it is, and then later asked to name it, he calls out at once 'oota;' and when he hears an imitation of the crow of a rooster a fleeting smile occurs on the right side of the face alone while during the whole event the arms are moved violently about the ears and face.

"He understood what was said to him and tried to make his wants known."

In addition to the foregoing the following notes were made upon his cranial nerves:

III, IV, VI not involved.

Motor V and sensory V not involved.

Motor VII tonic spasms produced compression of the lips with irregular clonic movements.

VIII normal.

IX, X, XII slightly irregular movements of the tongue, throat, and palate.

XI very violent tonic and clonic spasms of the spinal accessory, the left more than the right.

I to IV spinal nerves: rotators slightly involved.

V to VIII spinal nerves: tonic spasm, adducting arms, flexing forearms, supinating forearms, extending wrists, flexing fingers: The flexing spasms alternate with some extensor spasm and there are also twitching, oscillating and rhythmic movements, causing the head to be twisted and retracted.

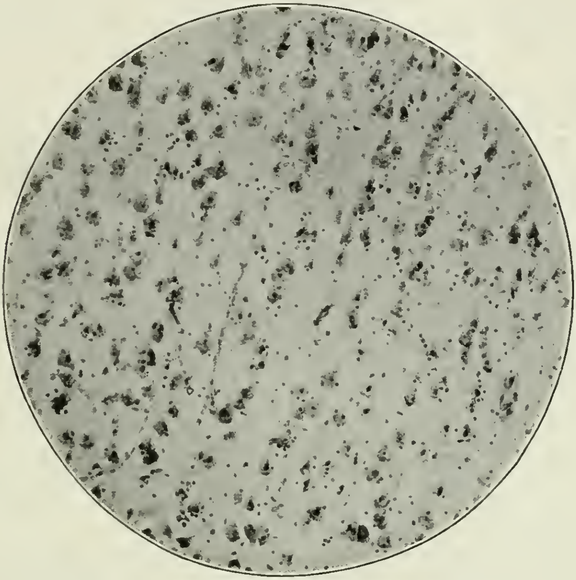

Fig. 6.—Posterior central convolution; arm area × 200.

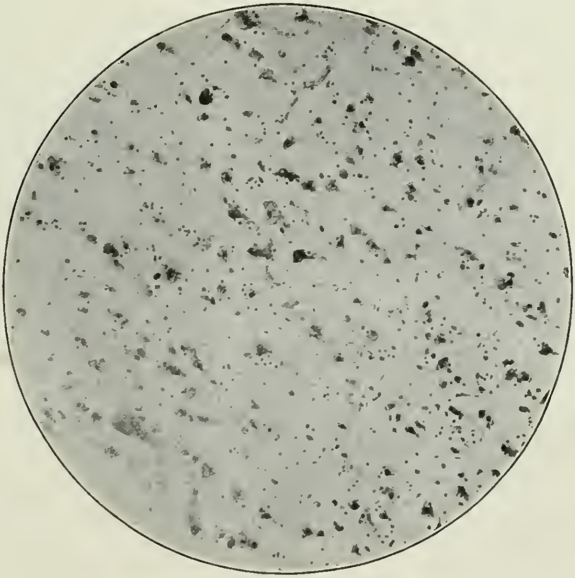

Fig. 7.—Anterior central convolution; leg area × 200.

The most violent movements seemed to be thus involving the neck and arms, and therefore it was thought possible to produce some relief by resecting the posterior roots of this region.

The operation was undertaken with great care by Dr. A. S. Taylor, but the child suddenly stopped breathing and died on the table.

Operation (reported by Dr. A. S. Taylor).

A left unilateral laminectomy was done, involving the 5th, 6th and 7th cervical vertebræ. There was no special difficulty in doing the laminectomy, but there was far more profuse hemorrhage than usual.

The dura was exposed when he suddenly stopped breathing. The heart continued to beat for some time. Artificial breathing was kept up for some time, and saline infusion was given when the heart gave signs of failing, but all to no purpose.

As to the cause of death, the hemorrhage was undoubtedly one factor. The operation had taken only twenty minutes up to that time, so it would not seem fair to hold the anesthetic nor the time consumed in any way responsible.

The unknown factor in the result might be termed lymphatic diathesis, or some of the other names with which ignorance is properly clothed.

Pathological Findings (by Dr. Gere). Examination of the specimen, upon which the clinical and pathological studies of this case rest, showed to the naked eye a brain of apparently normal development in a child of six years, symmetrical in its lateral halves, the convolutions, generally, were deep and full and exhibited no evidences of localized atrophy.

Measurements of the cerebrum, taken after fixation in formalin, may be given as 15 cm. in its anteroposterior diameter, while the greatest transverse diameter measured 11 cm. The weight cannot be accurately given, but, after immersion, one cerebral hemiphere weighed one-half kilo.

The membranes appeared normal except for a mild basilar meningitis, more apparent microscopically than to the naked eye. The areas inspected include the motor cortex, the postcentral convolution, the thalamic and subthalamic regions, the basal ganglia, red nucleus besides sections through each of the nuclei of the cranial nerves; the spinal cord was also sectioned at different levels.

In observation of the motor cortex attention is directed in a general way to a rather indiscriminate arrangement of cells below the layer of medium-sized pyramidal cells to an apparent diminution in the number of cells of large size, to the difficulty in defining, strictly, cell lamination, and to the distortion of individual cells with, in many instances, an absence of dendritic processes.

Interspersed are to be found many cells preserving their normal pyramidal form and others in varying stages of degeneration.

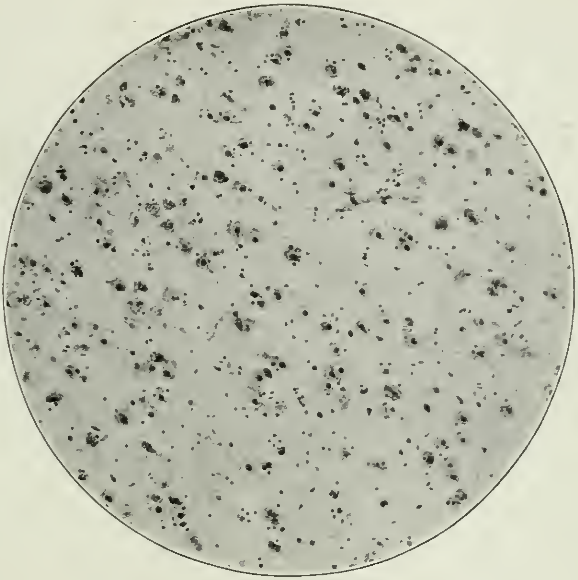

FIG. 8.—Posterior central convolution; leg area × 200.

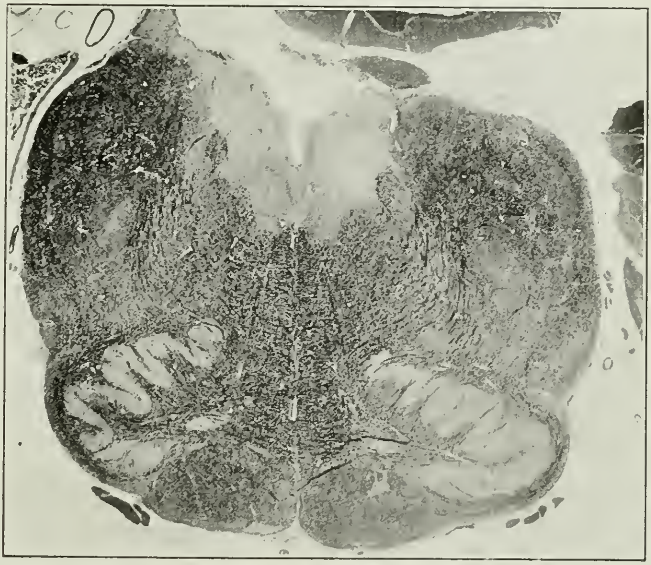

FIG. 9.—Medulla; region of twelfth nerve.

The degenerative process is shown by a tigrolysis varying up to a complete destruction of the chromophylic granules; the nucleus in many of the partly degenerated cells is preserved and placed eccentrically, while the remaining granules are piled up at one pole. A deficiency in size, number, and arrangment of the cells of Betz is very striking.

Inspecting the lamina in order, the plexiform layer does not appear to be disturbed and the cells of the second and third layers are normal except for a few more or less degenerated cells in which the processes are not strongly marked. The layers of large pyramidal cells are not always well defined but appear confused. In the deeper layers of the cortex are many degenerated cells.

In the postcentral convolution cell lamination is far more distinct and the disturbance is present in a slighter degree, though here too, are many degenerated cells lying deep in the cortex.

The thalamic and subthalamic regions and the basil ganglia show nothing remarkable in cell formation and arrangment, and there is no degeneration of cells of the nuclei of the cranial nerves, but the eccentric position of the cell nucleus with the peculiar clumping of the chromophylic granules is, in many cases, pronounced.

Though the clinical history makes note of difficulty in swallowing and of convulsive movements of the face, both the hypoglossal and facial nuclei of each side present no abnormality.

Other nuclei in the region of the hypoglossal, namely, the ninth and tenth, in both the motor and sensory divisions appear entirely normal; nor are changes demonstrable in the sixth, fifth, fourth or third nuclei.

The cells of the anterior horns of the spinal cord from the first cervical segment to the sacral region are normal, but the posterior column nuclei show a few worn cells similar in appearance to those observed in the postcentral and motor areas.

The corticospinal pyramidal system shows no degeneration, but there is a deficiency of medullated fibers in one lateral pyramidal tract throughout the cord. Similarly there is a deficiency without degeneration of the posterior columns, particularly in the columns of Goll in the upper lumbar, the dorsal and cervical regions. In the medulla the arcuate fibers and median lemniscus are well developed and present no pathological changes.

The third and lateral ventricles of the brain are not dilated, and exhibit a thickened subependymal tissue with a tendency to gliosis, though the ependyma itself appears normal, and this is also true of the Sylvian aqueduct, which is very irregular in outline and sacculated.

In the region of the posterior corpora quadrigemina and placed ventral to the aqueduct of Sylvius there appears a formation resembling an obliterated canal by ependyma.

Changes similar and more intense are to be observed in the fourth ventricle, especially in its posterior extremity, where a condition of gliosis undoubtedly exists.

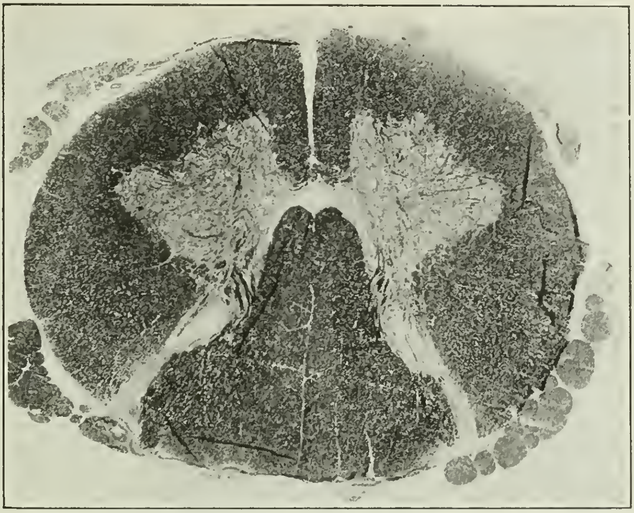

FIG. 10.—Spinal cord, cervical region.

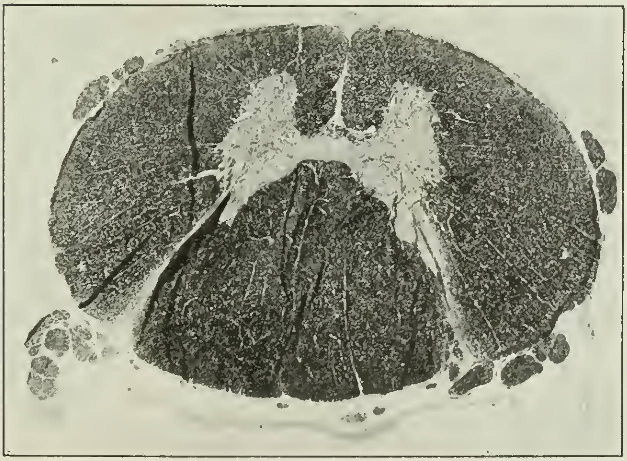

FIG. 11.—Upper dorsal cord.

The choroid plexuses present no particular pathological change. The cerebral vessels are the seat of marked changes which consist of thickened walls, distended perivascular lymph spaces containing many deposits of round cells.

Examination of the cerebellum fails to demonstrate any departure from the normal structure of that organ.

The observations in the above report were confirmed by Dr. James Ewing and Dr. T. H. Ames.

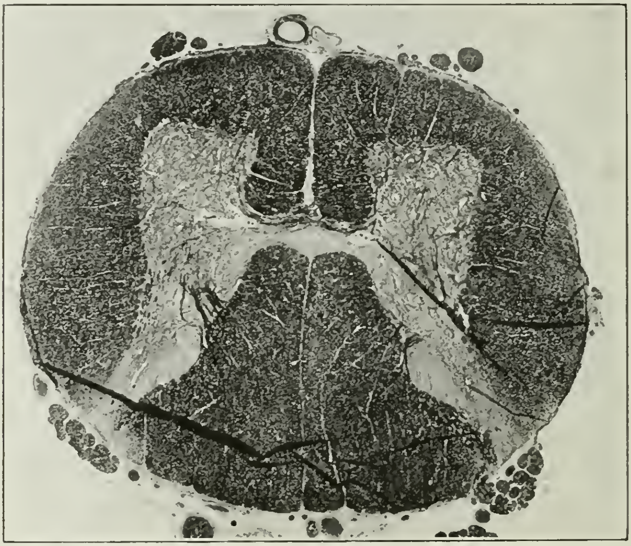

Fig. 12.—Lumbar cord.

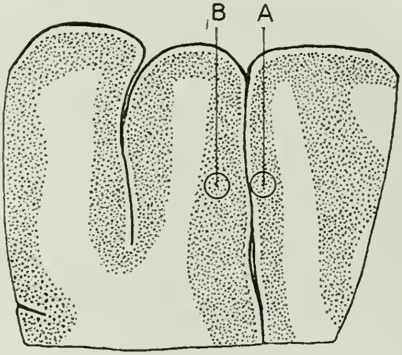

Fig. 13.—Anterior (*B*) and posterior (*A*) central convolutions—arm area—showing location of areas photographed.

The conclusions from this case are that the patient had at the fourth month a low grade infectious polioencephalitis affecting especially the motor cortex and impairing the sensori-motor mechanism, *i. e.*, the dendrites and fibrils. This led not to paralysis but to irregular motor discharges and loss of muscular control.

The existence of an abnormally fine pyramidal tract is probably due to some slight involvement of the cells of Betz, and this might perhaps explain spasticity and weakness, but not the various types of mobile spasm seen in the case reported here.

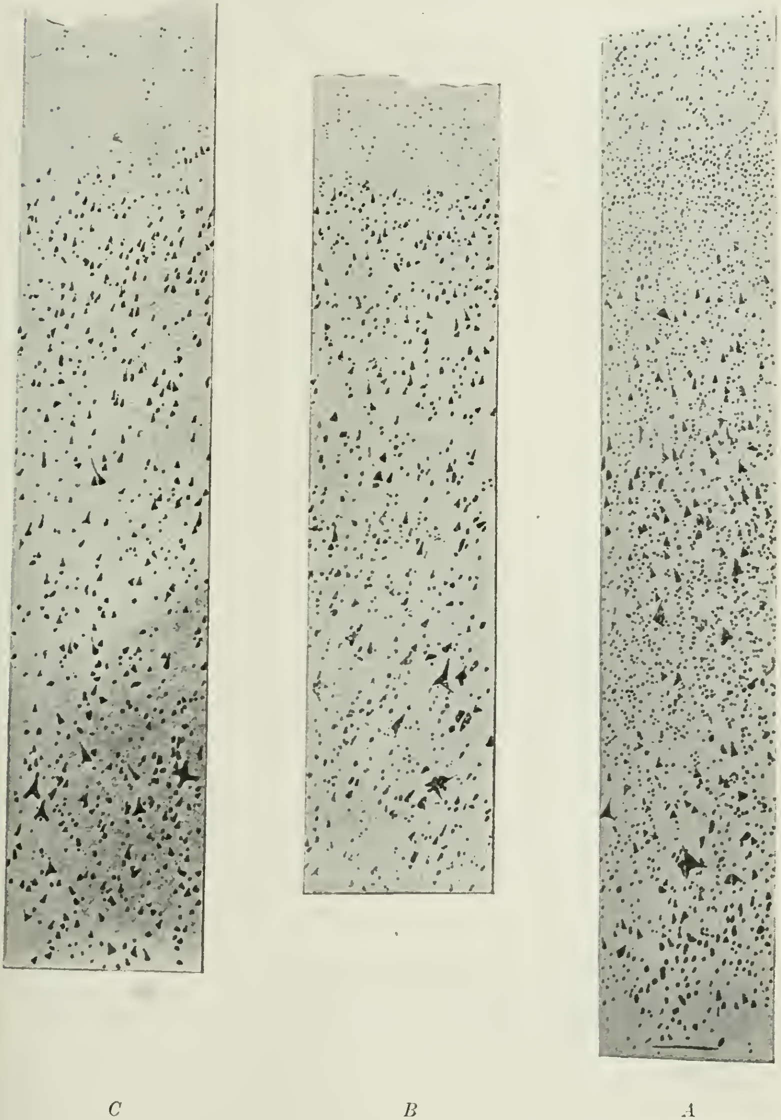

Fig. 14.—*A*, section through the anterior central convolution of a healthy brain; *B* and *C*, sections through the anterior central convolutions of two cases of cerebral spastic hemiplegia with intact pyramidal tracts. One sees in both cases that the deep layers are hardly affected, while the superficial layers are markedly atrophied. (H. Vogt.)

The subject of cerebral hemiplegia and diplegia without involvement of the pyramidal tracts is discussed in full with bibliography by Dr. H. Vogt.[1] In these cases, sometimes at least, the spastic paralysis seems due to atrophy of the superficial layers of the cortex with intact cells of Betz (Fig. 13). In our case it was not so much atrophy of particular layers, but various irregular displacements, degenerations, and focal atrophies. This would explain the irregular motor discharges.

The cortical changes that were found are sufficient to explain the spasmodic symptoms, and as these lesions were induced by some infection four months after birth it is a fair inference that they were primary and not secondary factors in the disease. We believe that they give us an indication of the pathological anatomy of the chronic degenerative myoclonic and myotonic spasms.

It seems to be fairly well established that the chronic, coarse, jerky, ataxic tremors are due to involvement of the cerebellar rubrospinal and extrapyramidal tracts. Such involvement is seen in paralysis agitans, multiple sclerosis, and midbrain and cerebellar disease.

But the clonic and tonic spasms such as are seen in spasmodic tics, torticollis, hereditary chorea, and myoclonias especially are cortical and due to defects and displacements of the cells of the central and precentral convolutions.

This view is supported by the fact that cortical changes are found in chronic and hereditary chorea, in myoclonus epilepsy and in certain localized degenerative tics.

The case presented clinically some of the features of Little's disease, with clonic and tonic spasms, but there was in our case no real paralysis and no involvement of the pyramidal or extrapyramidal tracts, at all adequate to explain the essential features of the symptoms.

A study of the types of cerebral infantile diplegia without anatomical findings has been first and elaborately made by Dr. William G. Spiller.[2]

A full bibliography of this subject is given as stated above by Dr. H. Vogt.

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[1] Lewandow's Handbruch de Neurologie, vol. iii, p. 295.

[2] Jour. Nerv. and Ment. Dis., 1898, p. 81; Univ. Penna. Med. Bull., January, 1905, by Dr. John H. W. Rheim; AMER. JOUR. MED. SC., December, 1909, and later by Berghinz, Revista di Clinica pediatrica, 1903, p. 416.

THE RELATION OF THE HYPOPHYSIS TO CERTAIN CLINICAL MANIFESTATIONS AND THE THERAPEUTIC APPLICATION OF ITS EXTRACTS.[1]

By Joseph L. Miller, M.D.,
CHICAGO.

During the past ten years there has developed a very extensive literature dealing with the role of the hypophysis in the animal economy. No attempt will be made to even review this investigation, but rather to consider only certain clinical manifestations which may be associated with disturbances in the hypophysis and the therapeutic application of its extracts. In this group may be considered acromegaly, dystrophia adiposogenitalis, or Fröhlich's syndrome, possibly adiposis dolorosa, or Dercum's disease, diabetes insipidus, and glycosuria.

It has been very clearly shown that the hypophysis is essential to life. Animals survive its complete removal only a few days, or at most a few weeks (Paulesco, Cushing, Biedl). When the posterior lobe alone is removed, permanent recovery without symptoms or disturbance of development occurs. As shown by Cushing and his colleagues, when only a portion of the anterior lobe is removed the animal may recover, but gradually develops a group of disturbances resembling very closely Fröhlich's syndrome as observed in man. The animal becomes very fat, the hair is thinned, atrophy of the testes or ovaries occurs, and the sexual activity is lessened or disappears. In the case of puppies there is failure of skeletal development and adiposity and sexual infantilism. It is apparent from these observations that it is the anterior lobe of the hypophysis that is essential to the life of the animal, its complete removal resulting in death, its partial removal in developmental disturbances. On the other hand it is only the extracts of the posterior lobe that have been demonstrated to be therapeutically active. Strictly speaking, this active substance is only present in the pars intermedia of the posterior lobe. This extract when administered intravenously or intramuscularly to man affects the cardiovascular system, the kidney, uterus, urinary bladder, intestine, and the secretion of the mammary gland.

Acromegaly. Marie, in 1886, first called attention to the probable relation between acromegaly and the hypophysis. Previous to this time mention had been made of the increased size of the hypophysis in pathological giants. Changes in this organ have no doubt been responsible for many of the giants in history, as a study of the sculpture on certain French and Italian churches shows that the giants figured there are in reality acromegalic individuals. When certain disturbances of the hypophysis occur early in life, gigantism follows, these same changes arising after maturity gives rise to acromegaly. It is stated that after castration there is a hyperplasia of the hypophysis, and it is well known that many eunuchs attain unusual height.

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[1] Read before the Chicago Institute of Medicine, January, 1916.

Without entering into a detailed discussion of this subject it may be said that at the present the generally accepted view is that acromegaly, like gigantism, is due to overfunctioning of the anterior lobe of the hypophysis. This may be accompanied by an actual enlargement of this lobe or simply by an increase in the specific glandular secretory cells. There is some evidence to show that certain types of dwarfism may be due to hypofunctioning of the anterior lobe. Quite numerous feeding experiments on young animals with anterior lobe substance have failed to show any general modification of growth, but increased rapidity of growth of the sexual organs (Goetsch). Feeding the posterior lobe has no effect on growth.

DYSTROPHIA ADIPOSOGENITALIS, OR FRÖHLICH'S SYNDROME. This condition, first described by Fröhlich in 1901, had as its chief clinical manifestations, adiposity, scant growth of hair, dryness and lowered temperature of the skin, trophic disturbance of the nails. When it occurs before maturity, failure of development of the bony skeleton, infantilism or sexual atrophy, in woman lessened or absent menstruation, and in man impaired sexual desire. While acromegaly and Fröhlich's syndrome thus differ materially in their clinical manifestation the two groups of disturbances may be present in the same individual. Many acromegalic individuals are adipose, have less sexual power, etc. According to Creutzfeld, sexual atrophy is observed in 36 per cent. of acromegalics and adiposity of the Fröhlich type in 1.5 per cent. of cases. The association of these three disturbances of development might lead one to infer that they had a common origin, *i. e.*, were due to disturbance in the same portion of the hypophysis. Inasmuch as one of these, acromegaly, is quite certainly due to disturbance of the anterior lobe, is it not probable that all of these developmental abnormalities have the same origin? Fröhlich, Fischer, Cushing, Falta and, in fact, practically all writers on this subject, have ascribed Fröhlich's syndrome to disturbances in the posterior lobe, this being in the nature of a hyposecretion. Cushing and his colleagues maintain that lessened functioning of the posterior lobe gives rise to increased sugar tolerance, and that this is a possible factor in the adiposity. It is difficult to see how, with the evidence at hand, such deductions are justified. The anatomical findings in the majority of these cases is of a new growth, either in the hypophysis or its immediate neighborhood—a type of tumor, however, different from that present in acromegaly, where adenomatous growths predominate, but rather destructive processes, as sarcoma, carcinoma, glioma, cysts, etc. In the 34 cases autopsied and reported by Biedl, 23 showed a tumor of the hypophysis and seven times a tumor in the region of the hypophysis. In at least one case the hypophysis was macroscopically normal. A study of the hypophysis in these cases has thrown very little light on the subject on account of the involvement of both lobes, either directly by the growth or indirectly by pressure or circulatory disturbance. The rare but still occasional association of adiposity with acromegaly might be interpreted as speaking against a common origin, viz., the anterior lobe for these two disturbances. These two conditions, however, are both developmental in character, one selecting the bony skeleton, the other the soft parts. It would not be more unusual, as Strada has stated, than the occasional association of myxedema and hyperthyroidism in the same individual. It is not necessary, however, to conclude that lessened secretion of the anterior lobe is responsible for the Fröhlich syndrome. There may occur a modification of the secretions due to a change in the character of the cells in the anterior lobe, as has been noted during pregnancy, where there occurs a great increase in the chromophobe cells with marked change in their histological character and quite probably change in the character of their secretion. At the same time there is a corresponding reduction of the chromophil cells. Accompanying these changes there is often a tendency to adiposity and especially rather marked and characteristic thickness of the face. The most convincing evidence, however, that Fröhlich's syndrome is due to the anterior lobe is furnished by the experimental findings in dogs. Removal of the posterior lobe is not followed by any serious consequences, the animals recover and later fail to show any anomalies of growth (Paulesco, Cushing, Ascola). However, when a considerable portion of the anterior lobe of a young dog is removed, and the animal recovers from the operation, he later develops the Fröhlich syndrome of delayed development, adiposity, and failure of sexual development. This evidence is very conclusive and to my mind far outweighs all our other information. While it is too early to say that Fröhlich's syndrome if associated with the hypophysis must be due to disturbances of the anterior lobe, it seems highly probable that eventually this will prove to be the case. The anterior lobe would then be responsible for all developmental anomalies; the function of the posterior lobe to furnish secretions which affect the cardiovascular apparatus, the kidney, the uterine, intestinal, and urinary bladder contractions and the secretion from the mammary gland.

Organotherapy in the treatment of Fröhlich's syndrome has not given very definite results. Cushing has reported a few cases where the administration of the entire hypophysis has caused reduction in weight and an improvement in the mental condition. Reported changes in the mental condition in this class of patients must be accepted with a certain amount of reserve, as the parents or friends of the mentally defective are usually most optimistic when an effort is made by the physician to improve conditions. Cushing, in his cases, has administered 9 grains daily in divided doses of the powdered entire gland. Patients with hypophyseal tumor and Fröhlich's syndrome, after operative removal, have been relieved of the pressure symptoms, but little change has occurred in the adiposity, growth of hair, or sexual condition.

ADIPOSIS DOLOROSA, OR DERCUM'S DISEASE. Only passing mention will be made of the possible relation of this condition to the hypophysis. Falta has collected from the literature 11 cases with autopsy. Three of these had hypophyseal tumors and 4 others on microscopic examination pathological changes of a variable character. Hyperplasia of the cellular elements of the anterior lobe was found in some and in others increased connective-tissue formation. Even more constant pathological changes have been detected in the thyroid of these individuals, and it is too early to state whether either or both of these glands have anything to do with Dercum's disease.

DIABETES INSIPIDUS. Magnus, Schaefer, and Herring first called attention to the diuretic action of extracts from the posterior lobe. This action, they reported, is partly due to dilatation of the renal vessels and in part due to direct stimulation of the renal cells, and apparently independent of any direct effect on blood-pressure. The diuresis continues long after the blood-pressure has returned to normal, and could still be excited after repeated injections, which result in a fall in pressure. In some instances diuresis occurred without increase in the size of the kidney, showing that it could not be due to renal dilatation but probably a result of increased activity of the renal cells, although, as a rule, dilatation of the renal vessels was associated with the increased urinary output. In these first experiments Schaefer and Herring worked with cats, using the extract intravenously and report quite constant evidence of diuresis. In dogs, however, in 7 out of 19 experiments, instead of diuresis, a diminished flow of urine was observed. With rabbits 2 out of 16 had a diminished urinary output after the intravenous injection of the extract. They explain this phenomenon by the presence of both a constrictor and dilator substance for the renal vessels; when the former predominates lessened urinary output results. When given subcutaneously to cats, diuresis was observed in only 25 per cent., of the tests, and when given by mouth, diuresis was never observed. To show the fallacy of therapeutic reasoning, after the publication of Schaefer's work, extracts of the hypophysis were placed on the market and recommended as diuretic when taken by mouth. At this time we made some clinical observations with this extract and found that even when given in very large doses it had no diuretic action. Von Velden has shown that pituitrin, when given subcutaneously in doses of 0.5 c.c. to normal individuals, never excites diuresis, but, on the other hand, lessens the urinary output. This reduction at times may reach 50 per cent. During the past three years, at Cook County Hospital, we have studied the effect of pituitrin given subcutaneously in considerable number of cases of both normal and nephritic individuals, and in none of these have we been able to demonstrate a diuretic action. When any effect was observed on the urinary output it was invariably a reduction. From observations made in a patient with diabetes insipidus, using intravenous injection, it would appear that lessened urinary output results from this method of administration. Von Velden has also shown that following its use there is a marked reduction in the Nacl output but no constant effect on the phosphorus or nitrogen excretion.

This effect of posterior lobe extract is in perfect harmony with the findings in diabetes insipidus, and furnishes additional evidence that one of the activities of the hypophysis is to inhibit the activity of the kidney.

Diabetes insipidus may be produced experimentally by a variety of procedures. Bernard first demonstrated that puncture of the floor of the fourth ventricle just anterior to the glycosuria center would cause marked polyuria. Kahler reports there is no part of the cerebellum, pons, or medulla where experimental lesions may not excite marked polyuria. In addition cutting the greater splanchnic nerves in dogs gives rise to marked polyuria.

Clinically the most frequent cause of diabetes insipidus is lesions of the cerebrum, tumors at the base of the brain, and especially syphilitic basilar meningitis. That lesions of the hypophysis are a frequent cause of diabetes insipidus has long been suspected as diabetes insipidus is a frequent complication of acromegaly and dystrophia adiposogenitalis. It is very frequently associated with bitemporal hemianopia, a finding highly suggestive of a hypophyseal lesion. Kraus in 34 cases with bitemporal hemianopia found associated diabetes insipidus in 7 and Steinhaus in 50 cases, diabetes insipidus in 11. Simmonds, in Hamburg, has recently reported the interesting observation that in 500 autopsies he found 9 metastatic carcinomas, all in the posterior lobe of the hypophysis, and in 3 of these there was a history of diabetes insipidus. He refers especially to the frequency with which metastases are found in the hypophysis in mammary carcinoma. Erdheim has also reported diabetes insipidus due to a metastic growth in the hypophysis from a primary breast tumor. At present I have made under observation a patient who was operated on for carcinomaof the breast a year ago and who is now complaining of a marked polyuria, and my attention has recently been called to another case with diabetes insipidus associated with a mammary carcinoma.

These observations are of special interest by reason of the tumor being found in the posterior lobe. On account of the hypophysis being encased in the sella it is often difficult to determine when a tumor is present, whether the symptoms arise from the lobe involved, or as a result of pressure on the uninvolved portion. In several of Simmond's cases, however, the tumor was so small that it could have exerted little if any pressure. It is also only reasonable to assume that the effect on the lobe would be to lessen its functional activity. This point is of considerable importance as following the reports on the supposed diuretic action of the pars intermedia, Schaefer, Frank, Cushing and others have endeavored to explain hypophyseal diabetes insipidus on the overactivity of the posterior lobe. Animal experimental work does not furnish any very clear-cut evidence. After complete hyposectomy there is, as a rule, only a transient polyuria lasting two or three days. In a few of Cushing's dogs this was prolonged for a week. With complete removal of either the anterior or posterior lobe this same transient polyuria was observed, but never after any of the removals was there a permanent marked polyuria. These results are the same as those obtained by Schaefer after stimulation of the hypophysis with the thermocautery, as after this procedure a polyuria of three or four days' duration was observed. As far as can be determined from the literature no one after partial or complete removal of the hypophysis has produced a permanent polyuria resembling diabetes insipidus. Cushing's work shows, however, that when one of these polyuric dogs received hypodermically an extract of the posterior lobe that with few exceptions it was followed by a lessened output of urine. Thus furnishing evidence that in dogs, as in man, in conditions of polyuria extracts of the posterior lobe reduced the urinary output.

The most conclusive evidence that diabetes insipidus when associated with the hypophysis is due to lessened rather than increased secretion of the posterior lobe is furnished by clinical observation. Frank, Biack, Farini, Sereboullet, Hoppe-Seyler, von der Velden, Lichtwitz, Shomeyer, and others have shown that in diabetes insipidus the subcutaneous injection of extracts of the posterior lobe will lessen the urinary output 50 or more per cent. When 1 c.c. of pituitrin is given twice daily this lessened output may be maintained apparently indefinitely. With the diminished amount of urine there is an increased specific gravity, and, as C. Velder has shown, a lessening of the chloride elimination, but no material change in the total output of phosphorus or nitrogen. A patient recently under our observation had diabetes insipidus of eight years' duration, probably due to syphilis. The average urinary secretion was 5 liters. When given twice daily a subcutaneous injection of 1 c.c. of pituitrin there was a drop in urine to 3 liters with increase in specific gravity. The blood urea-nitrogen before the use of pituitrin was high (31 mg. per 100 c.c.). After the pituitrin had been used several days the urea-nitrogen fell to 22 mg. As this was a single observation it is of little value, but of interest as showing in this particular case with the reduction of water output there had been an increased urea elimination. Following a single intravenous injection of 0.7 c.c. the urinary output during the following twenty-four hours fell to 1100 c.c., and the patient stated that for the first time in eight years he had not risen in the night to urinate. Large amounts of pituitrin by mouth and 0.3 gm. doses of powdered anterior lobe by mouth were without effect.

Glycosuria. It is generally conceded that patients with acromegaly very frequently show either a transitory or permanent glycosuria. Borchard collected 176 cases of acromegaly from the literature in 63 (or 35.5 per cent.), of which sugar was found in the urine. In 5 additional cases there was a definite alimentary glycosuria. Schlesinger and Borchard and Cushing have reported single cases in which, in the later course of the disease, the lessened sugar tolerance was changed to an increased tolerance. Inasmuch as acromegaly is thought to be associated with hyperplasia of the posterior lobe, it might be assumed that this portion of the gland was responsible for the glycosuria. Cushing, however, expresses the view that the glycosuria observed in acromegaly is due to hyperplasia of the posterior lobe and that the increased sugar tolerance which may develop later is due to the hypoplasia of the posterior lobe, which he believes not infrequently occurs late in the course of the disease. Accepting the theory that Fröhlich's syndrome is due to hypoplasia of the posterior lobe, he believes that a factor in the adiposity is the increased sugar tolerance. In other words, he considers the posterior lobe as playing an important role in sugar metabolism. When overactive, lessened tolerance occurs, and when underactive, an increase of tolerance above the normal. He reports an invariable glycosuria in rabbits after intravenous injection of extracts from the posterior lobe. It may be said that these views of Cushing have not been generally confirmed by other observers. During the past year Forschbach and Severin have studied the sugar tolerance in acromegaly, Fröhlich's syndrome, and in hypophyseal tumors without developmental disturbances. Their results show there is a lack of constancy of the sugar tolerance in each of these conditions. Two patients with acromegaly, one of fifteen years' duration, showed marked increased sugar tolerance, another of twelve years' duration a lessened tolerance; two Fröhlich syndromes had a normal tolerance, and 3 cases of hypophyseal tumors, without developmental disturbance, an increased tolerance. Bernstein reports two Fröhlich syndromes with normal sugar tolerance and two others with increased sugar tolerance. Recently, Woodyatt, with his new method, studied the sugar tolerance in a patient of mine with diabetes insipidus and Fröhlich's syndrome, of eight years' duration and did not detect any variation from the normal. Believing that this sugar tolerance was due to a hormone arising in the posterior lobe, Weed, Cushing, and Jacobson after sectioning the cord and stimulating the hypophysis were able to produce glycosuria. Keeton and Becht have repeated this experiment, but instead of cutting the cord have severed the splanchnics and have been unable to cause a hyperglycemia by stimulating the hypophysis. They did show, however, that electrical stimulation of the hypophysis in dogs gave rise to a hyperglycemia, while this did not occur in stimulation of the adjacent structures.

Experimental efforts to produce glycosuria in animals by injecting extracts of the hypophysis give conflicting results; Borchard obtained positive results in 28 out of 35 rabbits and 5 out of 7 dogs. Pal's results were negative, Franchini with 22 rabbits had 2 positive results. Lewis and Miller injected 30 rabbits, 15 with anterior and the same number with positive lobe extracts, and only 1 animal in each series developed glycosuria. Very recently Bernstein reported that he was unable to produce glycosuria by extracts of either the anterior or posterior lobe.

From these conflicting results it is apparently impossible to determine the role, if any, of the hypophysis in sugar metabolism. The readiness with which glycosuria appears after a multitude of disturbance to the brain adds to the confusion. Falta reports transitory glycosuria in 20.8 per cent. of skull fractures of convexity and 23.8 per cent. of basal fractures, and in 9.3 per cent. of severe head injuries without fracture. Glycosuria is common in tumors in various parts of the brain, and especially of the floor of the fourth ventricle. The readiness with which glycosuria appears in animals after anesthesia renders it difficult to draw conclusions as to the cause of glycosuria after operative measures in the hypophysis.

Galactogogue Action. Ott, in 1910, discovered the galactogogue action of the hypophyseal extract. He found that when given intravenously to goats or cats there appears within one-half minute a marked increase in the amount of milk excreted from the breast. When given subcutaneously to lactating women similar results are obtained. The milk after the administration of the hypophyseal extract is especially rich in fat. This might appear to have some practical value in increasing and improving the quality of milk output. It has been shown, however, that in the second milking after the injection there is a reduction below normal in the quantity of milk, and the percentage of fat is decreased so that the total output and fat content in the twenty-four hours is not increased. Simpson and Hill have shown that an immunity is rapidly acquired in goats after its prolonged use, the effect on the quantity and fat content becoming much less apparent. This galactogogue substance is present only in the posterior lobe. Herring has made the interesting observation that the anterior lobe of the hypophysis of some reptiles contains a galactogogue agent. The galactogogue action of the extract does not run parallel to its vascular action, and the belief is that it acts directly on the secretory cells of the mammary gland.

The hypophysis during pregnancy undergoes a hypertrophy and hyperplasia. These changes, however, are apparently confined to the anterior lobe, the chromophobe cells being changed into a special cell of pregnancy, which after confinement reverts back again to the normal chromophobe cell. The posterior lobe, which is the source of the galactogogenic substance, does not, as far as is known, undergo any change either during pregnancy or lactation.

Osteomalacia. The etiology of osteomalacia is still undetermined. It has been ascribed by different observers to disturbed function of the ovaries, suprarenals, parathyroid, and hypophysis. These results are so conflicting that it is impossible to say whether any of the ductless glands are concerned in its development. Bossi, Christolette and others have reported improvement after the use of adrenalin, and Bab has reported beneficial results after the use of pituitrin, and Pal after feeding with extracts of the anterior lobe.

Use in Cardiovascular Condition. Pituitrin when given intravenously, much less constantly when given intramuscularly, causes a gradual and rather prolonged rise in blood-pressure with slight slowing of the heart. The rise in pressure is due to vascular constriction, the drug acting directly upon the musculature in the vessel wall, resembling in this respect barium chloride. This slowing of the heart is due chiefly to stimulation of the cardio-inhibitory mechanism and partly to direct effect on the heart muscle. It is generally thought that, as a result of direct action on the muscle, the heart's contractions are strengthened. Wiggers, however, believes its effect on the heart is depressive at least in the majority of instances.

Judging from the literature, hypophyseal extracts have not been used extensively in cardiac condition. A few references have been made to their value in the cardiovascular disturbances in the acute infection. More clinical observations must be made, however, before it can be determined whether pituitrin is of real value in these conditions.

Action on the Uterine Musculature. Extracts of the posterior lobe of the hypophysis stimulates uterine contraction by its direct action on the unstriated muscle. Apparently the reaction of the uterus varies somewhat in different animals. In guinea-pigs it has a marked action on both the pregnant and virgin uterus; in rabbits only in the pregnant uterus. During the past four years there has developed a very extensive literature on the value of pituitrin and allied preparation in stimulating the uterus during labor. The results, on the whole, are quite favorable, and, provided a proper selection of cases is made, is largely free from danger. It should only be used in the second stage of labor when the os is well dilated. In the earlier stages of pregnancy it is contraindicated, as it may excite uterine contractions without dilatation of the os. When the os is dilatated and uterine contractions are feeble, 1 to 2 c.c. of pituitrin intramuscularly may be of considerable value. The pituitrin may also be of value in postpartum hemorrhage.

Effect of Intestinal Peristalsis. Bayer and Peter have shown that the posterior lobe extracts cause first a lessening of the tonus and peristaltic action of the intestine, soon followed, however, by increased tonus and greatly increased peristalsis. After the use of the extract, peristalsis may be excited in an isolated piece of intestine in which all rhythmical contraction had ceased. Klotz and others have recommended extracts of the posterior lobe for postoperative peritonitis. Here absence of vascular tone in the splanchnics, of toxic origin, is largely responsible for the distention. The extract by acting directly on the musculature of the vessel wall, and at the same time stimulating intestinal peristalsis, should tend to relieve the condition. He reports decidedly beneficial results in twenty patients. He used pituitrin intravenously, diluting it with normal salt solution and injecting very slowly. He has also used, with beneficial results, intramuscular injections of 2 c.c. Klotz and others have also used pituitrin with apparent good results in the treatment of mild intestinal obstruction and in postoperative intestinal stasis. During the past two years I have used pituitrin, 1 c.c. intramuscularly, in the treatment of the abdominal distention complicating pneumonia, but have never observed any beneficial results. Perhaps if used intravenously desirable action might be obtained.

Action on the Bladder. Frankl Hochwart and Fröhlich, in 1910, reported marked increase in bladder contraction in cats after the use of pituitrin. Here again it affects directly the unstriated muscle. During the past few years several favorable reports have appeared on its value in causing spontaneous empyting of the bladder and thus avoiding catheterization after confinement (Cahor, Schirmer), and following operation on the pelvic organs (Jasches). The usual dose, 1 to 2 c.c., is given intramuscularly.

Control of Hemorrhage. On account of its action on unstriated muscle we can readily see how pituitrin might be of value in uterine hemorrhage of certain character, especially postpartum hemorrhage. It is more difficult to explain why it should have an effect on hemorrhage elsewhere. It is true it acts as a vasoconstrictor, and agents of this character do not necessarily affect all vessels in the same manner. Adrenalin, for instance, is a powerful vasoconstrictor, but dilates the coronary arteries. A vasoconstrictor which affected certain bloodvessels without raising the general blood-pressure might have a hemostatic effect in organs where vasoconstriction occurred. As a rule, however, vasoconstrictors by raising blood-pressure interfere with the fixation of the clot, and are, therefore, contraindicated in hemorrhage. Celilli, in 1914, recommended posterior lobe extracts, given subcutaneously for the control of hemorrhage in nasal and throat operation. Since then there has been confirmation of his results. Rist, in 1913, and later Minet and Martin recommended this agent for the treatment of hemorrhage in pulmonary tuberculosis. The former gave 0.5 c.c. intravenously. It is a question whether with a severely ill tuberculous patient it would be advisable to give the drug intravenously on account of the danger of exciting vomiting and vertigo. Kahn and Gordon, who have studied the effect of pituitrin on blood coagulation, report reduction of the coagulation time by half; in this respect it behaves like adrenalin (von den Velden). If time should show that pituitrin acts as a hemostatic it will probably be explained on its effect on coagulation rather than its vasoconstrictor action.

This concludes the therapeutic application of hypophyseal extracts. It will be noted that these results were obtained only with extracts from the posterior lobe. They must be given subcutaneously, intramuscularly, or intravenously to obtain any action. By mouth, like adrenalin, they are inactive. Perhaps time will show that the anterior lobe may be of value in stimulating growth and sexual activity, but experimental and clinical evidence of this action is still lacking.

In closing, mention should be made of the use of posterior lobe extracts in the treatment of bronchial asthma. On account of pituitrin having an effect on blood-pressure somewhat resembling adrenalin, several publications have appeared recommending its use in bronchial asthma. This is apparently wrong. Pal, Fröhlich and Pick, Baehr and Pick, and others have shown that pituitrin produces bronchial spasm, while the relief given by adrenalin, is due to its power to dilate the bronchi. Baehr and Pick have also shown that when combined with adrenalin the pituitrin action on the bronchi is inhibited by the adrenalin. This probably accounts for the beneficial action of a proprietary preparation containing pituitrin and adrenalin recommended for the treatment of asthma.

As a complete bibliography may be found in Biedl's *Innere Sekretion*, 1913, 2d edition, only a few of the more recent references will be given.

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THE VALUE OF THE AMBARD QUOTIENT IN THE ESTIMATION OF RENAL FUNCTION.

By Leon Jonas, M.D.,
WOODWARD FELLOW IN PHYSIOLOGICAL CHEMISTRY,
AND
J. Harold Austin, M.D.,
ASSOCIATE IN MEDICINE, UNIVERSITY OF PENNSYLVANIA.

(From the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.)

In this study are reported the results obtained from the determination of Ambard's quotient of renal efficiency (as modified by McLean) in a series of clinical cases with and without nephritis. Ambard's quotient was the outcome of a series of studies beginning with that of Ambard and Papin,[1] in 1909, upon the laws governing the concentration of urea in urine. Previous workers had noted the difficulty of securing a constant urea concentration in the urine of either man or animals even on carefully controlled diets. Ambard and Papin found, however, that in the dog an exclusively meat diet with as much water as the animal desires produces a urine of remarkably uniform urea concentration. This concentration of urea under these conditions is independent of the protein content of the diet and is the maximal urinary urea concentration for that animal. Any factor which unduly increases the animal's thirst, such as the feeding of bread or of salt, a diarrhea, or an inadequate supply of food, will, if water is freely available, disturb this relation in the urea excretion and lower the concentration of the urea in the urine. These authors further observed, however, that the kidney can eliminate a much larger amount of urea in a unit time if the secretion be accomplished at a lower concentration. When the renal parenchyma was sufficiently reduced experimentally the animal could eliminate urea only at a lower concentration. At this lower concentration, however, a very large amount of urea could be excreted as the result of a polyuria, only following the stimulation from an accumulation of urea in the blood. Ambard[2] showed that both in the dog and in man, if a constancy of the urea concentration in the urine is maintained, the square root of the urea eliminated in the urine during any unit of time is closely proportional to the concentration of the urea in the blood in any given individual, and that this law (Ambard's first law) holds for nephritis as well as for the normal kidney. The unit of time used for measuring the urea excretion must, however, be short (about an hour or less), since the continual variations in both the rate of urea excretion and the concentration of the blood urea will otherwise cause apparent discrepancies in their interrelations. Variations in the concentration of the urea in the urine alter, however, the relation between the rate of urea excretion and the urea concentration of the blood. An effort was made by Ambard[3] to define mathematically the effect of this factor of concentration. To do so, however, was not easy, because of the extreme difficulty of obtaining subjects in which, with varying urinary urea concentration, the blood urea concentration remained constant. After many examinations, two subjects in which these conditions were realized were observed, and from them Ambard concluded (second law) that if the blood urea remains at a constant concentration, the rate of urea excretion is inversely proportional to the square root of the urea concentration in the urine. The validity of this second law was by no means so well established by Ambard's work as was his first. On the basis of these two laws, Ambard and Weill[4] developed a formula into which was introduced with these two factors, in the relations stated, an additional factor designed to compensate for the variations in weight between different individuals arbitrarily selecting 70 kilos as the standard weight. They also adopted in this formula 25 gms. of urea per liter as the standard concentration of urea in the urine. In its complete form, Ambard's quotient is as follows:

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[1] Étude sur les concentrations urinarires, Arch. internat. de physiol., 1909, viii, 437.

$$\text{Constant} = \frac{\text{Ur.}^2}{D \times \frac{70}{\text{wt.}} \times \frac{\sqrt{c}}{25}}$$

Ur. — gm. of urea per liter of blood.
D. — gm. of urea excreted in twenty-four hours.
Wt. — wt. of individual in kilos.
c. — gm. of urea per liter of urine.

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[2] Rapports entre le taux de l'urée dans le sang et l'elimination de l'urée dans l'urine, Comp. rend. Soc. de biol., 1910, lxix, 411.

[3] Rapports de la quantité et du taux de l'urée dans l'urine, la concentration de l'urée du sang étant constante, ibid, 506.

[4] Les lois numériques de la secretion rénale de l'urée et du chlorure de sodium, Jour. de physiol. et de path. gén., 1912, xiv, 753.

For the sake of simplifying the calculation, and in order to make the quotient rise and fall with the renal efficiency instead of rising as the renal efficiency falls, and *vice versa*, as is the case with Ambard and Weill's constant, McLean[5] has transposed the original formula without altering its essential principle, so that it stands as follows:

$$\text{Index} = \frac{\text{Gm. urea per 24 hours } \sqrt{\text{gms. urea per liter urine}} \times 8.96}{\text{Wt. in kilos} \times (\text{gm. urea per liter of blood})^2}.$$

When Ambard and Weill's quotient = 0.080, the standard normal, McLean's index = 100. According to McLean this index should be above 80 when renal function is normal, and indices below 80 indicate more or less impairment of renal function.

It must be remembered that Ambard's formula is constructed on a purely empirical basis. The particular functions, the square and square root, being chosen not on any logical grounds but merely because, in a number of instances, under certain conditions, the use of these functions gave calculated results agreeing with the observed findings. Even though each of Ambard's laws hold independently under the partially constant conditions of the original studies, it might be questioned whether the combination of these two laws as expressed in their formula would necessarily hold under varying conditions. That their formula does frequently accord with the observed facts has been shown by Ambard and Weill, by McLean and others. On the other hand, McLean, using his modification, sometimes obtains indices in normal individuals exhibiting the wide range of from 80 to 250. Addis and Watanable[6] conclude that the rate of urea excretion in man varies under physiological conditions, and that these variations cannot be completely explained by the variations in the amount of urea in the blood and urine. Pepper and Austin,[7] in dogs (using, however, total nitrogen instead of urea), found enormous variations in the quotient in different animals and in the same animals under different conditions. The question probably arises, therefore, as to whether Ambard and Weill's formula or its modification is the precise expression of the fundamental physiological law that governs the relation between the concentration of urea in the blood and in the urine and the rate of urea excretion, or whether it is merely a crude approximation to the actual quantitative relation, a sort of diagram that indicates the direction in which changes in one of the factors concerned will influence the others. This question can best be answered by an investigation of the quotients obtained in the same normal individual at different times under different conditions and by a comparison of the quotients obtained from different normal individuals. Only if these quotients consistently approximate a constant can we accept the formula as representing anything more significant than a sort of diagram of these relations.

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[5] The Numerical Laws Governing the Rate of Excretion of Urea and Chlorides in Man, Jour. Exper. Med., 1915, xxii, 212.

[6] Rate of Urea Excretion; a Criticism of Ambard's and Weill's Law of Urea Excretion, Jour. Biol. Chem., 1916, xxiv, 203.

[7] Experimental Studies of Urinary and Blood Nitrogen Curves after Feeding, Jour. Biol. Chem., 1915, xxii, 81.

A study of the quotient derived by applying Ambard's formula as modified by McLean to a number of individuals with presumably normal kidneys shows at once that the quotient obtained is anything but constant.

CHART I.—CASES WITH PRESUMABLY NORMAL KIDNEYS.

No.	Name.	Date.	Age.	Sex.	Diagnosis.	Urine urea per 24 hours.	Urine urea per liter.	Blood urea per liter.	Weight (kilo).	Index.	Blood-pressure.
1	Kelly	Jan. 17, 1916	37	M	Perihepatitis; pleurisy	17.90	9.23	.23	70	145	
		Jan. 25, 1916				20.98	11.90	.30	72	113	
		Jan. 21, 1916				20.08	5.22	.22	70	116	
2	Wa.	Jan. 5, 1916	24	M	Gastric neurosis; constipation	20.62	10.31	.19	56	280	90–68
		Jan. 8, 1916				27.67	2.82	.24	54	132	
		Jan. 10, 1916				20.20	4.80	.16	54	267	
3	VanS.	Feb. 1, 1916	29	M	Endothelioma of lymph nodes	20.9	12.0	.21	61	242	126–76
		Feb. 5, 1916				28.27	12.61	.24	61	255	
4	Ma.	Feb. 1, 1916	46	M	Angina pectoris	17.18	7.68	.21	75	128	104–70
		Feb. 8, 1916				29.46	6.71	.27	75	124	
		Feb. 15, 1916				16.78	8.16	.24	75	99	
5	Ki.	Jan. 27, 1916	..	..	Epilepsy	23.04	7.68	.23	70	153	
		Jan. 21, 1916				23.22	5.53	.33	70	64	
6	Li.	Nov. 8, 1915	50	M	Sciatica	11.46	17.40	.19	75	147	115–85
		Nov. 18, 1915				9.18	22.97	.22	77	79	112–74
		Nov. 30, 1915				24.25	26.25	.25	77	219	112–68
7	Gr.	Dec. 20, 1915	26	M	Bronchial asthma: subacute bronchitis	34.80	14.04	.27	72	222	
		Dec. 23, 1915				31.78	10.45	.24	71	224	
8	Em.	Nov. 21, 1915	42	M	Syphilitic hepatitis	24.52	26.7	.30	75	185	117–65
9	Mi.	Jan. 5, 1916	18	M	Chronic arthritis; mitral regurgitation with compensation	9.60	20.87	.22	63	124	122–70
10	At.	Jan. 5, 1916	22	M	Pulmonary infarction; subacute mitral and aortic regurgitation with compensation	14.16	19.15	.31	58	96	116–54
11	Ka.	Feb. 29, 1916	63	M	Headache	14.66	22.88	.31	54	120	115–75

In this study, which was made on patients in the medical wards of the University Hospital, periods of 72 minutes were employed (or in a few instances slightly larger periods up to 160 minutes) and the blood withdrawn from an arm vein 36 minutes after the period began. The urea was determined by the urease method described by Van Slyke and Cullen.[8]

The cases may be divided into three groups: First, cases in which there is no clinical or laboratory evidence of nephritis, nor of marked cardiovascular disease, nor of cardiac decompensation; the findings in these cases are tabulated in Chart I. Second, cases

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[8] A Permanent Preparation of Urease and its Use in the Determination of Urea, Jour. Biol. Chem., 1914, xix, 211.

CHART II.—CASES WITH NEPHRITIS.

No.	Name.	Date.	Age.	Sex.	Diagnosis.	Urine urea per 24 hrs.	Urine urea per liter.	Blood urea per liter.	Weight.	Index.	Blood-pressure.	Eye-grounds.
1	Br.	Feb. 25, 1916	44	M	Advanced glomerulonephritis; cardiac decompensation	12.17	10.35	1.13	77	2	180 to 140	Sclerosis; retinitis.
		Mar. 4, 1916				10.83	8.20	1.05	80	3		
		Mar. 8, 1916				10.51	5.88	1.09	80	2		
2	McC.	Nov. 30, 1915	53	M	Advanced chronic nephritis	27.15	8.58	.91	66	12	210 to 150	Retinal exudate and edema.
		Dec. 15, 1915				20.93	17.16	1.14	66	9		
		Dec. 17, 1915				33.00	13.85	.98	64	18		
		Dec. 20, 1915				15.25	13.45	1.17	64	5.7		
3	Jo.	Nov. 29, 1915	35	M	Chronic glomerulonephritis	20.73	19.20	.75	62	23	180 to 112	
		Dec. 31, 1915				9.78	13.59	.51	62	20		
4	St.	Nov. 4, 1915	24	M	Advanced glomerulonephritis	18.02	4.00	.45	64	25	172 to 126	Neuroretinitis; exudate and hemorrhage.
		Nov. 15, 1915				18.01	4.02	.42	59	27		
		Nov. 29, 1915				16.23	2.75	.24	61	23		
		Dec. 3, 1915				23.75	5.11	.30	60	140		
5	O'D.	Apr. 17, 1916	39	F	Advanced glomerulonephritis	21.02	8.08	1.93	112	1.3	250 to 160	Marked neuroretinitis.
6	Wa.	Feb. 1, 1916	24	M	Chronic endocarditis; chronic nephritis; intermediate	55.4	16.10	.90	62	40	160 to 120	
7	An.	Jan. 5, 1916	47	F	Advanced glomerulonephritis	8.07	12.60	.83	68	5	272 to 141	Sclerosis; retinitis.
8	Ba.	Mar. 6, 1916	15	M	Glomerulonephritis; intermediate	16.38	13.76	.49	47	60	165 to 115	Negative.
9	Hi.	Nov. 27, 1915	55	M	Chronic glomerulonephritis	20.23	26.63	.48	64	64	210 to 110	
10	Ya.	Mar. 11, 1916	26	F	Chronic nephritis; intermediate	16.5	9.16	.46	47	44	140 to 110	Negative.
11	Mo.	Feb. 8, 1916	45	M	Glomerulonephritis; intermediate	31.2	21.42	.39	83	103	185 to 135	Neuroretinitis.
12	Ch.	Mar. 9, 1916	36	M	Glomerulonephritis; intermediate	15.35	15.75	.37	67	61	176 to 110	Sclerosis.
13	Dav.	Apr. 17, 1916	21	F	Chronic degenerative nephritis	13.07	13.35	.37	58	59	160 to 130	Negative.
14	Wh.	Feb. 2, 1916	24	F	Glomerulonephritis; intermediate	19.18	2.93	.31	49	62	198 to 175	Early retinitis.

with definite evidence of more or less severe nephritis; tabulated in Chart II. Third, a few cases in which there is no definite nephritis; but in which there is more or less vascular disease or cardiac decompensation or both; tabulated in Chart III.

CHART III.—CASES WITH VASCULAR DISEASE.

No.	Name.	Date.	Age.	Sex.	Diagnosis.	Urine urea per 24 hours.	Urine urea per liter.	Blood urea per liter.	Weight (kilo).	Index.	Blood-pressure.
1	Bo.	Nov. 22, 1915	50	F	Sclerotic hypertension; cardiac decompensation	32.76	11.7	.34	56	15	200–110
2	Ro.	Feb. 29, 1916	57	M	Arteriosclerosis	9.2	7.1	.31	60	38	142– 85
3	Hur.	Nov. 8, 1915	63	M	Myocardial weakness	16.45	2.94	.30	84	33	122– 83
		Nov. 18, 1915				11.25	4.50	.24	85	43	145– 98
4	Da.	Feb. 27, 1916	59	M	Sclerotic hypertension	17.41	6.00	.37	54	47	170– 12
5	Ki.	Nov. 2, 1915	36	M	Chronic myocarditis	22.07	4.32	.28	79	64	121– 72
		Nov. 16, 1915				10.72	22.33	.38	79	36	
		Nov. 16, 1915				26.55	14.62	.30	..	176	

CHART IV.

Name.	Diagnosis.	Date.	Urine urea per liter.	D. Urine urea per 24 hours.	Ur. Blood urea per liter.	$\frac{Ur}{\sqrt{D}}$
Van S.	Endothelioma; lymph nodes	Feb. 1, 1916	12.00	20.90	.21	.045
		Feb. 5, 1916	12.61	28.27	.24	.045
Ma.	Angina pectoris (very mild)	Feb. 1, 1916	7.68	17.18	.21	.051
		Feb. 8, 1916	6.71	29.46	.27	.050
		Feb. 15, 1916	8.16	16.78	.24	.058
McC.	Advanced nephritis	Dec. 17, 1915	13.85	33.00	.98	.171
		Dec. 20, 1915	13.45	15.25	1.17	.300
St.	Advanced nephritis	Nov. 4, 1915	4.00	18.02	.45	.106
		Nov. 15, 1915	4.02	18.01	.42	.099
		Dec. 3, 1915	5.11	23.70	.30	.062

			Blood urea per liter.	D. Urine urea per 24 hours.	C. Urine urea per liter.	$D \times \sqrt{C}.$
Ke.	Perihepatitis	Jan. 17, 1916	.23	17.90	9.23	54
		Jan. 21, 1916	.22	20.08	5.22	46

Inspection of the cases tabulated in Chart I, cases in which presumably the kidneys are normal, shows the wide variation that is observed in the index in the same individual on different occasions and in different individuals. We may profitably examine certain of these cases from another point of view. If those instances of repeated examinations on the same individual where the urea concentration in the urine was approximately constant be chosen we find five examinations (see Chart IV) on two normal individuals. If to the data of these examinations Ambard's first law be applied it will be found to be confirmed in the first case, the ratio of $\frac{\text{Ur}}{\sqrt{\text{D}}}$ being constant in the two examinations on this case and also in the first two examinations of the second case. Among the nephritic cases five examinations from two cases exhibit approximately constant urinary urea concentration, but Ambard's first law does not hold in these cases. This is, perhaps, due to progression of the renal impairment in the first case and amelioration in the second.

If we select from our data those non-nephritic cases with repeated examinations showing constant blood urea concentration for the purpose of verifying Ambard's second law we can find only one case (see Chart IV). In this case Ambard's second law is but poorly supported. This finding is quite in harmony with the results previously quoted from Pepper and Austin; it is when there is variation in the urinary urea concentration that Ambard's formula most frequently gives unsatisfactory results. However, since variability in the concentration of urea in the urine is the rule and not the exception, this defect may seriously impair the value of Ambard's formula as a gauge of renal function under ordinary clinical conditions. The variability which we have found in the constant at repeated examinations of the same non-nephritic case or in comparing with each other one group of non-nephritic cases leads us to conclude that Ambard's formula is not a mathematically accurate expression of the behavior of renal function as regards urea excretion, but that it is merely a crude diagrammatic indication of certain relations between blood urea and urea excretion and urinary urea concentration.

The question must arise, however, whether Ambard's quotient or its modification, in spite of this objection that may be urged against it, is of value clinically as an index of renal function. If we can demonstrate that the quotient gives with reasonable constancy, information evidently more consistent with the clinical condition and subsequent course of the patient than does the careful inspection of those factors separately that go to make the quotient, we might well employ the quotient for diagnostic and prognostic purposes. On the other hand the determination of the index, because of the necessity for great accuracy in collection of the urine, is a much more difficult procedure to carry out than is the simple estimation of the blood urea, and more important still there are possibilities of undetected errors occurring through the loss of a small quantity of urine. Hence, unless some definite advantage can be urged in favor of the quotient as compared with the simple blood urea considered with due regard to the character of the urinary excretion, the latter would appear to be the safer criterion in clinical diagnosis and prognosis.

Inspection of our results would lead us to conclude that if we are to accept McLean's normal blood urea figures, 0.20 to 0.50 gms. per liter as correct, then the index is a more delicate measure of renal impairment than is the blood urea.

In our nephritic group, 10 out of 23 examinations show a blood urea within McLean's normal figures and 21 out of 23 give figures for the index below 80, which, according to McLean, indicates impairment of renal function. The clinical picture would lead us to suspect impairment of renal function in those cases. If, however, we accept Tileston's and Comfort's[9] figures for blood urea, 0.35 gms. per liter, or Folin and Denis's[10] urea figures, 0.23 and 0.28 gm. per liter as normal, then in out studies the index no longer possesses any advantages over the blood urea.

Inspection of Chart I will show that we have never found a blood urea in a normal or non-nephritic individual above 0.35 gm. per liter under ordinary conditions, and we have, accordingly, accepted this figure as the upper normal limit, which is in accord with the views of Tileston and Comfort. Accepting 0.35 gm. per liter as the upper limit of normal, then it is readily seen that in our nephritic cases blood urea alone gave as satisfactory evidence of impairment of function, as did the index except in the third examination of St. and in the case of Wh.

In the case of Wh. and the third examination of St. the index gave information which the blood urea alone would have failed to show.

Inspection of Chart III shows that in cases in which in all probability the only impairment in renal function is the result of arteriosclerotic changes or of renal passive congestion, the index may show pronounced depression while the blood urea remains within normal limits. There is evidence to suggest, therefore, that the index is at least in certain cases a more delicate gauge of renal impairment than is the blood urea. It is at least possible, however, and indeed highly probable, that for clinical purposes of diagnosis and prognosis these cases present rather an argument against the use of the index and for the blood urea than the reverse. It is in part because the estimation of the blood urea often helps to distinguish true nephritis from arteriosclerotic lesions, or from congestion of the kidney, that it is of value in these cases. Clearly for this purpose the index would be of less value, being too sensitive and too readily reduced by arteriosclerotic condition and by passive congestion as well as by nephritis.

On examination of Chart III, which consists of frank cases of nephritis, one fails to see the marked variability in the index in individuals in whom more than one examination has been made that was noted in the non-nephritic cases. This tendency to constancy of the index in cases of nephritis with impaired function has also been emphasized by McLean.

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[9] The Total Non-protein Nitrogen and the Urea of the Blood in Health and Disease as Estimated by Folin's Method, Arch. Int. Med., 1914, xiv, 620.

[10] On Uric Acid, Urea, and Total Non-protein Nitrogen in Human Blood, Jour. Biol. Chem., 1913, xiv, 29.

The patient St. shows marked rise of the index on the fourth examination, due to the elimination of a urine of higher urea concentration and to a higher urea output which have most probably been caused by large doses of infusion of digitalis which he received between the time of the second and third examination.

Finally, it seems possible that in conditions in which there is either an extremely high nitrogenous intake or in which there is very rapid tissue catabolism, the blood urea may be raised above 0.35 gm. per liter, although renal function is quite normal, and that this may be accompanied by an increased rate of urea elimination in the urine with a normal index. In such cases the index would be a better gauge of the state of renal efficiency than would the blood urea alone. McLean has induced just such a condition by the administration of urea to normal individuals. Under ordinary circumstances, however, such conditions do not obtain, and our conclusion would be that, as a rule, the blood urea alone is a better guide in ordinary clinical diagnosis and prognosis than is the index.

CONCLUSIONS. 1. The Ambard formula in its original form or as modified by McLean does not express precisely the law of renal function with respect to the elimination of urea, and this is particularly true as regards the effect of urinary urea concentration.

2. The upper limit of blood urea in non-nephritic and normal individuals under ordinary conditions of diet and life is about 0.35 gm. urea per liter of blood. Figures higher than this are, under ordinary conditions of diet, to be considered evidence of impaired renal function.

3. Using McLean's modification of Ambard's formula, it was found that in the great majority of nephritic cases a lowering of the index was accompanied by an elevation of the blood urea above normal limits, 0.35 gm. per liter, and that the index afforded no information of diagnostic or prognostic value that could not be as readily deduced from the blood urea alone.

4. In certain cases the index was found to be lowered when the blood urea was within normal limits. This was especially true in arteriosclerotic cases and in cases with cardiac decompensation, which probably detracts from the clinical value of the index as compared with that of the blood urea rather than the reverse, since it is of importance to distinguish between cases of vascular and renal character.

5. In the determination of the index there is a possibility of error arising from undetected incomplete collection of the urine, which cannot occur in the simple blood urea estimation.

6. The urea index estimated repeatedly in the same individual exhibits wider variations in the normal or non-nephritic individual than in the nephritic.

7. For purposes of ordinary clinical diagnosis and prognosis the estimation of blood urea is a more reliable and more useful guide than is the urea index or the Ambard quotient.

THE EXPECTORANT ACTION OF AMMONIUM CHLORIDE.[1]

By Warren Coleman, M.D.,
NEW YORK.

(From the Department of Applied Pharmacology, Cornell University Medical College, and the Second Medical Division of Bellevue Hospital.)

Ammonium chloride is used so extensively in the treatment of respiratory affections that it is important to determine whether it does or does not possess an expectorant action.

All of the text-books on pharmacology which I have consulted regard ammonium chloride as an expectorant. Cushny, however, merely says that "ammonium chloride is generally credited with acting on the secretion of the bronchial mucous membrane, which it is said to render more fluid and less tenacious and at the same time to increase considerably." The majority of text-books on therapeutics recommend ammonium chloride in the treatment of respiratory diseases.

In the discussion of Dr. Miller's[2] paper on "The Clinical Value of Expectorants," read before the Association of American Physicians, Dr. Meltzer said "ammonium chloride is, I believe, a reliable remedy for increasing secretion and expectoration." Other speakers expressed themselves in similar vein.

Yet on the basis of a few experiments upon lower animals in which important factors were not controlled, it has been denied that ammonium chloride in the usual therapeutic doses acts as an expectorant upon patients suffering from bronchitis.

In view of the doubt which has thus been created, I decided to reinvestigate the action of ammonium chloride upon the bronchial secretion in man. Patients with acute or chronic bronchitis were selected as subjects for the experiment. The objections which have been brought against the validity of such experiments do not appear to me to be fundamental. They are based upon the assumption that to act as an expectorant a drug must increase the total quantity of secretion within arbitrarily fixed periods. The generally accepted definition of an expectorant is a drug which facilitiates the expulsion of mucus from the respiratory passages. Under this definition a drug may soften and release mucus from the walls of the bronchi without increasing the quantity in twenty-four hours. In fact, if we assume a healing effect of the drug upon the inflamed mucous membrane, as is generally done, the amount of secretion for the twenty-four hours may at times be actually diminished. Yet this does not invalidate the conclusion that the drug is an expectorant in the sense that it makes expectoration easier.

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[1] Presented before the Association of American Physicians, Washington, May 11, 1916.

[2] Tr. Assn. Amer. Phys., 1914, xxix, 139.

Experiments on Laboratory Animals. The experiments on the action of ammonium chloride upon the bronchial secretion of laboratory animals may be summarized as follows:

They were carried out on dogs and cats. The preliminary operations were done under chloroform or ether, or both. The trachea was severed in all experiments; in most of them the mucous membrane was exposed for direct observation. The anesthesia was prolonged by chloral, chloretone, or urethane.

The conclusions concerning the expectorant action of the drugs studied (ammonium chloride, ammonium carbonate, antimony, squills, senega, apomorphin, ipecacuanha, and pilocarpin) were based either upon inspection of the mucous membrane or the weight of a piece of filter paper before and after it had been placed in contact with the mucous membrane, or by the amount of secretion which could be led off from the trachea through a tube. When there was no visible increase in the secretion and no increase in the weight of the filter paper the conclusion was drawn that the drug under investigation did not possess expectorant properties.

All of these experiments are open to objections which vitiate the conclusions drawn from them. The objections are as follows:

No proof is offered that the anesthetics employed (chloral, chloretane, urethane) were without influence upon the bronchial secretion.

The evaporation of water from the exposed mucous membrane of the trachea is left entirely out of consideration. The control of this factor is of the highest importance.

The assumption is made that all expectorants produce a visible increase in the bronchial secretion under the conditions of the experiments.

Until these objections have been met the negative results obtained cannot be considered as conclusive.

One of the arguments advanced to disprove the expectorant action of ammonium chloride is that a large proportion of the drug is converted to urea in the liver—according to Biedl and Winterberg,[3] from one-half to four-fifths—and that with the usual therapeutic doses the amount reaching the general circulation would be too small to affect the viscosity of the bronchial secretion.

More recent experiments, however, do not support the observations of Biedl and Winterberg. Wolf and Osterberg[4] studied the influence of ammonium chloride upon the ammonia nitrogen curve in the urine. The experiment was performed upon one of the authors. The normal ammonia nitrogen excretion was first determined and then 5 grams of ammonium chloride was taken in one dose. The result was as follows:

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[3] Arch. f. d. ges. Physiol., 1901–02, lxxxviii, 140.

[4] Biochem. Ztschr., 1912, xl, 193, 234.

Average normal output of ammonia nitrogen = 0.366 gm. .	0.732 gm.
Ammonium nitrogen in two days after ammonium chloride =	1.537 "
Difference	0.805 "
Nitrogen in 5 gms. ammonia chloride	1.308 "

This experiment shows that 52.5 per cent. of the ammonium chloride was eliminated by the kidneys alone in two days. Of special interest is the fact that the ammonia nitrogen curve in the urine reached its highest point within two hours after the ammonium chloride was taken. The urea excretion (expressed in terms of per cent. of total nitrogen) fell from the daily normal of 79.50 per cent. to 75.40 per cent. on the day the ammonium chloride was taken. The ammonia nitrogen in the urine rose from 4.10 per cent. to 10.24 per cent. on the same day.

These results, together with the progressive increase in the ammonia nitrogen content of the sputum, make it clear that in man little if any ammonium chloride is changed to urea in the liver.

THE PLAN OF EXPERIMENT. The plan of experiment which I followed was: First, examination of the sputum of patients suffering from acute or chronic bronchitis for the ammonia nitrogen content, and second, observations upon the subjective symptoms referable to the respiratory passages following the administration of ammonium chloride.

If it can be proved that ammonium chloride is excreted as such, in appreciable quantities, by the bronchial mucous membrane, and if at the same time the secretion is more easily expelled, I believe that the expectorant action of the drug will thereby be established.

Seven persons, including Dr. B. F. Weems, house physician, a nurse in training, and myself were used as subjects of the experiment. All were suffering from acute or chronic bronchitis.

The sputum was collected before the administration of the ammonium chloride was begun and at various times thereafter. It was put at once into bottles containing chloroform and placed in an ice-box to prevent decomposition.

Subjective observations were made only by Dr. Weems and myself.

The doses of ammonium chloride varied from ½ grain every two hours to 5 grains every two hours.

THE AMMONIA NITROGEN IN THE SPUTUM.[5] Standard solutions were prepared containing 0.01, 0.02, 0.025, 0.03, 0.035, 0.04, 0.045,

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[5] I wish to express my appreciation of the kindness of Dr. Stanley Benedict in making the chemical tests.

0.05, 0.06, 0.07, 0.08, 0.09, and 0.10 mgm. of ammonia nitrogen in 5 c.c.

A sample of sputum from each patient as centrifuged and 1 c.c. of clear fluid was measured into a test-tube; this was diluted to 5 c.c. with water, treated with 10 drops of Nessler's reagent, and compared with the above standards (treated with an equal amount of Nessler's solution).

Typical results follow:

N. W. A. The ammonium chloride was taken in ½-grain doses every two hours.

Before taking	0.02
After 10 grains	0.015
" 30 "	0.035
" 85 "	0.050

Davey. The ammonium chloride was taken in 5-grain doses every two hours.

Before taking	0.03
After 15 grains	0.025
" 60 "	0.06

Roselle. The ammonium chloride was taken in 5-grain doses every two hours.

Before taking	0.02
After 15 grains	0.03
" 60 "	0.095

There was a marked contrast in the ammonia nitrogen reactions of the saliva and sputum. The reaction of the saliva was always faint even under full dosage of ammonium chloride and when the intensity of the reaction in the sputum was progressively increasing.

SUBJECTIVE OBSERVATIONS. Dr. Weems. Mild bronchitis of only several days' duration. Treatment begun on the second day of the attack with ½-grain doses of ammonium chloride at two-hour intervals. Distinct loosening of the sputum and diminished roughness of the tracheal and bronchial mucous membrane followed. The taste of ammonium chloride was evident in the sputum at first, later the sense of taste for all substances was blunted.

Self observations: Severe bronchitis of several weeks' duration. Treatment was begun at once, but was suspended from time to time and resumed for the purpose of repeating the experiment. The ammonium chloride was taken at first in ½-grain doses every two hours and later in doses of 5 grains at the same intervals.

Whenever the drug was stopped the sputum became less abundant, more tenacious, and more difficult to expel, and a sensation of dryness or tightness developed in the chest. When the drug was resumed the opposite effects were observed. The action of the drug always developed within one-half to one hour. The experiment was repeated too often to permit of doubt as to the accuracy of the observations.

Another fact of special importance was noted. For twelve or thirteen hours after a dose of $\frac{1}{2}$ grain (the drug having been taken at two-hour intervals during the previous twelve hours) the taste of ammonium chloride, which is unmistakable, was evident in the sputum as it passed through the mouth. This observation possesses double significance: it identifies the form in which ammonium chloride is excreted by the bronchi (which was not established by the chemical analysis) and it demonstrates that the excretion of ammonium chloride is relatively slow in man—that is, in $\frac{1}{2}$-grain doses every two hours it is ingested more rapidly than it is eliminated by all channels through which it leaves the body. The rate of excretion bears upon the question of the supposed transformation of ammonium chloride to urea by the liver which has been referred to.

Mode of Action. The mode of action which appears most plausible is that ammonium chloride, during or after its excretion, or both, lessens the viscosity of the mucus, partly through increasing the water of secretion and partly through solvent action, and that then the normal mechanisms of removal come more readily into play. Being less viscid the mucus is carried by ciliary action more rapidly toward the upper respiratory passages and finally is expelled from them by the act of coughing.

One of the experiments of Henderson and Taylor[6] may be interpreted as corroborating this view, though they cited it to disprove the expectorant action of ammonium chloride.

According to their protocol they exposed the mucous membrane of the trachea of a dog to view and measured the rate at which charcoal travelled through ciliary action. They found that human saliva could travel at the same rate, but that the actual rate depended upon the thickness of the layer. Weak solutions of ammonium chloride and ammonium carbonate, directly applied, did not increase the rate of the saliva beyond that of the charcoal. The addition of water increased the rate to a maximum as effectively as did the ammonium salts. They concluded that the viscosity of the saliva was of more importance than the salts in solution.

If it be assumed that ammonium chloride in its passage through the bronchial wall increases the water of secretion, the contention in favor of the expectorant action of the drug receives strong support from this experiment. According to this experiment, ammonium chloride does not increase ciliary motion. The experiment also removes the necessity of seeking an explanation for the expectorant action of the drug in stimulation of the bronchial gland centres or in stimulation of peristalsis in the bronchioles.

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[6] Jour. Pharm. and Exp. Therap., 1910, xi, 153.

Summary. Clinicians generally believe that ammonium chloride is an expectorant. This action has been denied, however, on the basis of experiments on laboratory animals in which important factors were not controlled.

The action of the drug has been reinvestigated on patients suffering from acute and chronic bronchitis. The objections which have been raised to such experiments are not fundamental.

The excretion of ammonium chloride as such in the bronchial secretions has been proved.

Subjective observations have shown that ammonium chloride facilitates expectoration.

On the ground of these facts it is claimed that ammonium chloride is an expectorant within the definition of the term. It probably acts by increasing the water of secretion and softening the mucus.

A STUDY OF PROXIMO- AND ACRO-ATAXIA IN TABES DORSALIS.[1]

By Frederick B. Clarke, M.D.,
MILWAUKEE, WISCONSIN.

(From the Department of Neurology of the University of Pennsylvania.)

This study of ataxia in early cases of tabes was undertaken because of a recent paper published by an excellent observer,[2] in which it was stated definitely that in tabes dorsalis, ataxia of the proximal extremity of the limb occurred earlier and could be demonstrated before acro-ataxia or ataxia of the distal portion of the limb.

This hypothesis was used as a means of differentiating between tabes and the subacute combined degeneration of the cord occurring in pernicious anemia, it being asserted that in early tabes there was demonstrable ataxia of the proximal extremity of the limb, before acro-ataxia or ataxia of the distal portion of the limb occurred, differentiating it from the ataxia occurring in subacute combined degeneration of pernicious anemia which appears in the reverse order.

Such a statement, if correct, coming as it does at a time when the sequence of the development of symptoms occurring in pernicious anemia with cord changes is receiving a great deal of study, would afford valuable assistance in making a differential diagnosis.

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[1] Read by invitation before the Philadelphia Neurological Society, April 28, 1916.

[2] Hoover, C. F., The Significance of Acro-ataxia and Proximo-ataxia, Am. Jour. Med. Sc., 1915, cl, 651.

However, it does not quite fit in with the symptoms one would expect from the histopathological changes in the cord in the two conditions.

For the purpose of study of the ataxia in tabes, only very early cases were selected from those applying for treatment at the dispensary of the University of Pennsylvania in the service of Dr. William G. Spiller.

At the end of six months only ten cases were selected for this study, which were, with but one exception, in the pre-ataxic stage. I wish to emphasize that all cases studied represented early tabes, and by consulting the accompanying chart it is seen that cases with marked or even moderate incoördination in the performance of the usual tests for ataxia were not included. The chart also shows the symptoms upon which a diagnosis was made. It will be noted in the chart that all but three of these patients have been able to perform their usual avocation. The three exceptions quit work chiefly because of pain.

It may not be amiss to review hastily the present conception of the factors which enter into ataxia, or, better still, the incoordination of tabes.

Jandrässik,[3] in 1880, formulated the cerebral theory of ataxia. He believed that the centers for coördination and association in the brain were alone responsible for this symptom.

Raymond[4] enlarged this theory, especially as regards the psychological side, chiefly because the favorable results obtained by him in reëducation were attributed to the cerebral origin of the condition.

Frankel[5] in his monograph discusses the various theories, and arrives at the conclusion that ataxia is the result of interference with the centripetal fibers before they reach the brain.

Dejerine in discussing locomotor ataxia says that "Ataxia is central in the sense that the full activity of the central coördinating mechanism is profoundly modified by the disturbance of excitation which comes to it normally from the periphery. It is then not absolutely just to say that it is a modification of sensation from the periphery due to solution of continuity of the pathway for sensory impression to coördinating centers."

Oppenheim assumes that the coördination of muscular function is regulated mainly by centripetal impulses which do not become conscious sensations, and describes ataxia in this sense as sensory.

Comparison of the Regional and Anatomical Distribution of the Lesions in the Spinal Cord in Tabes Dorsalis and in Pernicious Anemia. In the subacute combined degeneration of the cord in pernicious anemia the thoracic region shows the first pathological changes; therefore, we should expect a disturbance of the sense of position and passive movement of all joints below this point, and the disturbance would be as early of the proximal joints as it would be of the distal.

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[3] Frankel (quoting Jandrässik), Tabes Dorsalis, p. 19.

[4] Frankel (quoting Raymond), Tabes Dorsalis, p. 19.

[5] Tabes Dorsalis.

The simultaneous involvement of the lateral columns of the cord would seriously interfere with this determination, since such an involvement necessarily leads to a hypertonicity of the limbs. In all except one of the few cases of pernicious anemia with cord changes which I have examined I could not determine whether proximo-ataxia existed for this reason. The one exception was a very early case in which there was increased reflexes and in which I was able to determine disturbances of the sense of position and passive movement in the shoulders and elbow joints when no other joints were involved.

In tabes beginning as the lesion usually does in the lumbar region of the cord, one should expect to find that the proximal joints of the legs would first show disturbance of joint and muscle sense, but such has not proved to be the case in the patients subjected to more delicate tests than those ordinarily used clinically.

Considering the lesions as to character and extent within the cord, there is found in tabes a distribution of the degeneration in the posterior columns quite different from that found in anemia. Regardless of whether one accepts the view of Obersteiner and Redlich or of Nageotte as to the primary lesion in the posterior roots in tabes, the changes in the posterior columns are axonal degenerations with glial replacement distributed in the white substance as a wedge-shaped area, the apex of which is directed toward the median commissure of the cord, and the base parallel to the posterior roots, leaving the cord substance along the posterior septum in the lumbar region free until later in the course of the disease.

The distribution of the lesions is the determining factor in the early clinical symptoms. It accounts for the interference with the sensory component of the reflex arc, resulting in loss of reflexes and a disturbance of muscle tone.

The involvement of the posterior roots and their ganglia produces trophic disturbances in the regions supplied, which, combined with the destruction of the reflex arc results in a hypotonic condition of the limb.

Fibers to Clarke's column and the cells themselves are early and constantly involved in tabes, with the result that the unconscious impulses from joints, muscles, and tendons are seriously impaired.

Hypotonia and loss of unconscious afferent impulses from skeletal structures are earlier signs in tabes than the loss of position sense and recognition of passive movements, and are of greater importance in the production of ataxia.

The cord changes in pernicious anemia, due as they are to some so far unknown hemolytic agent, shows an entirely different pathological character and anatomical distribution, which appears to be largely determined by the distribution of the blood supply. The lesion is a periaxonal degeneration beginning in the posterior column along the posterior median septum with involvement of the lateral columns. The pathological alteration consists primarily of a degeneration of the medullary sheaths and later destructive of the axis-cylinders with in some regions but little glial proliferation as evidenced by the reticular appearance of the section. The distribution of the lesion along the posterior septum leads to a definite clinical syndrome, which is: disturbance of afferent impulses from the skeletal structures; loss of vibratory sense; disturbance of stereognostic perception; inability to distinguish between two points of the compass.

From the anatomical location of the lesion in the two conditions and the greater intensity of the degeneration in the posterior columns earlier in pernicious anemia, with the resulting disturbance of function, we should expect that in pernicious anemia loss of the sense of position and passive movement must be earlier symptoms than in tabes, although static and dynamic ataxia are not demonstrable early symptoms. This naturally leads to the pertinent question as to why the degeneration in pernicious anemia, located in the cord in such position as to interfere seriously with the recognition of the impulses from the skeletal structure, does not produce early incoördination upon volitional movement. This, to my mind, is due to the fact that the lateral columns are also involved, producing a hypertonicity of the muscular apparatus, which is directly opposite to the hypotonicity in tabes. Therefore, one must consider hypotonicity as of great importance in the causation of the ataxia in tabes. An equally important factor is the loss of unconscious impulses of equilibrium which occurs early in tabes and relatively late in subacute combined degeneration of the cord in pernicious anemia.

Incoördination or ataxia is shown by the fact that upon volitional movements the object is not attained in the shortest way nor with the requisite amount of force, and insofar as it relates to the cord changes in tabes it is the result of an interference with centripetal pathways, which renders it distinct from asynergy of central origin. It is not alone a dynamic but static ataxia as well. Continual intervention with the sensory impressions which come from the objects around us as well as from moving parts of our bodies are important factors in the production of ataxia. There is no difference, insofar as ataxia is concerned, between the movements of a healthy person in the performance of some new complicated act, and the movement of a tabetic in the performance of an act familiar to him. Both are due to irregularity of muscular movement, the result of faulty knowledge of the proper inervation necessary for the performance of the act. Therefore, all movements to determine ataxia should be those with which the individual is familiar.

In addition to the ordinary movements used to determine ataxia, such as the finger to nose, the finger to toe tests, buttoning of clothing, Romberg's sign, etc., I have devised a system of charts to determine degrees of ataxia not sufficient to be brought out by the usual clinical means. By these charts I have endeavored to eliminate the action of certain muscle groups except those used in the performance of the test. While this is possible for practical purposes they are open to some degree of criticism or purely theoretical grounds.

The following methods were used for the upper extremity:

For the full arm movement a large sheet of paper is used upon which a circle three feet in diameter is drawn. Within this, by means of a rubber stamp, twenty-four circles are made, each being one inch in diameter and at equal distance from each other, there being two rows around the margin of the circle.

In the performance of this test the chart is placed against the wall, the center of the circle being on a plane with the patient's eye. He is then instructed to mark a cross with a pencil in the circle, being careful to start and stop the pencil mark on the margin of each circle. To determine disturbance of flexion and extension of the elbow, lines are drawn across a sheet of paper, an effort being made to start and stop the pencil mark on given base lines. In making this test the patient was seated at a table with the elbows resting on its surface, and the lines were drawn by a movement of the elbow.

For determining the coördination of the wrist a sheet of paper was used upon which were placed small circles one-fourth of an inch in diameter arranged in such a way that the lateral movements of the wrist were used in reaching the circles, within which a cross was made. It is in this test impossible to rule out some slight movement of the finger joints.

To determine incoördination of finger movement a figure of five rectangles was made with a rubber stamp, each side of a rectangle being one inch in length, the object of the test being to determine any degree of incoördination of movement made in tracing the lines of the figure. In this test as well as in the preceding one the elbow is fixed. Methods used for the lower extremities:

For the full leg movement a sheet of paper was used upon which circles one inch in diameter were made. On different parts of the surface sufficiently far apart to bring out all movements of the fully extended leg. In performing this test the patient stood on one foot, one arm being on a fixed support, to insure steadiness of the trunk and one limb, leaving one limb free for the test. A leather device closely fitting the big toe, and containing a marker, was used to place the mark within the circle.

To determine incoördination of the lower limb, as shown by dismetria in drawing lines, the patient was seated, thereby eliminating, largely, movements of the hip joint and with the device previously mentioned directed to draw lines on a plain surface, as was done in determining dismetria of the elbow-joint.

For the purpose of determining coördination of flexion and extension of the ankle joint and great toe a series of circles one-fourth of an inch in diameter were arranged in an arc, the extreme figures being eight inches distant from each other. The patient being seated and the limbs to be tested resting easily at right angles with the body, he was instructed, using the pointing device on the toe, to place a mark in the center of each circle.

Needless to say that the patients were all carefully instructed and allowed to perform the movements before the test was made.

The accompanying table will show graphically the various disturbances presented in each case.

It is seen that the most marked variability exists as to the predominance and frequency of any one symptom, and that ataxia, as shown by the Romberg, finger to finger, finger to nose, and toe to finger, tests have been relatively normal in all cases.

As regards ataxia in the execution of the full arm movement, it is seen that there is, in five cases, some slight disturbance, and in the same individuals there is more marked disturbance in the distal joints of the limb. Also that marked ataxia of the distal extremity of the limb was present in nine instances.

It is true that the finer muscular adjustments necessary in the performance of a complex act would show ataxic disturbances earlier than a less complicated movement, but certainly simple tracings over the lines of a rectangle is no more complex for the fingers than marking in circles would be for the full arm.

A surprising feature was the ability with which the greater number were able to use the full movement of the extended leg in the performance of the test, but all of the cases except one showed a variable degree of ataxia in the movement of the ankle and great toe. This exception was a well-trained athlete whose muscular coördination was perfect, although the patellar reflexes were difficult of determination even with reinforcement, and the tendon Achilles reflex was lost.

One important point brought out in the determination of the ataxia was the uncertainty and hesitation before beginning of the movement and evident difficulty with which the limb was stopped after the performance of the test was complete. This is the most important single factor in determining the degree of ataxia and does not show in the charts.

Conclusions. From a study of the anatomical distribution of the lesions in the cord in the two conditions, it is fair to conclude that ataxia, occurring in early tabes, is in a large measure the result of an interference with certain afferent fibers which results in hypotonia and from the loss of the afferent impulses concerned in equilibrium, with the subacute combined degeneration of the cord in pernicious anemia, it is due more exclusively to an interference with afferent fibers carrying impulses from the skeletal structures, *i. e.*, sense of position and passive movement and muscle sense. It may, I believe, also be assumed that the lesions in tabes by reason of their distribution, are of greater importance in the production

No.	Pupil.	Pain.	Sensory disturbance.	Disturbance over chest.	Bladder.	Blood Wassermann.	Romberg.	Gait.	Patellar reflexes.	Achilles reflexes.	At usual occupation.	Vibratory sense.
1 D	Argyl Robinson	In legs	None	Sense of constriction	Yes	Positive +	No	Slight ataxia	Lost	Lost	No	Normal
2 C	Left pupil Argyl Robertson	Marked in legs	None	Girdle sensation	Yes	+	No	Normal	Diminished	Active	Yes	Normal
3 C	Sluggish reaction to light	Variable in legs	Normal	Constriction of thorax	Yes	+	No	Normal	Diminished	Normal	Yes	Normal
4 H	Argyl Robertson	Pains in legs	Around waist	Constriction of thorax	Yes	+ + +	Slight	Normal	Decreased	Lost	No	Normal
5 P	Argyl Robertson	Pain, fifth nerve distribution	General	Moderate	Normal	Unknown	Slight	Difficulty at night	Lost	Lost	Yes	Marked disturbance over face and head
6 C	Pupils irregular	Pains in knee	Over chest	Around chest	Normal	+	Slight	Normal	Lost	Lost	Yes	Normal
7 A	Unequal and sluggish pupils	Marked	Normal	Normal	Slight	Negative	Slight	Normal	Normal	Lost	Yes	Decreased over legs
8 W	Left pupil Argyl Robertson	None	Normal	Normal	Normal	Negative	None	Normal	Markedly diminished	Lost	Yes	Normal
9 M	Pupils normal	Marked in legs	Normal	Normal	Yes	Negative	Slight	Disturbed at night	Lost	Markedly diminished	No	Decreased over legs
10 FP	Sluggish reaction to light	None	Cushion sensation over feet	None	None	Negative	None	Slight disturbance	Active	Absent	Yes	Normal

of ataxia than the lesions in pernicious anemia, and that hypertonicity tends to limit the degree of ataxia. From the clinical methods used, it is found that in tabes there is a more frequent and more marked ataxia in the distal than in the proximal articulations of the limb, and that the distribution of the ataxia cannot be used clinically as a means to differentiate tabes dorsalis from the subacute combined degeneration of the cord which occurs in some cases of pernicious anemia.

Joint sense.	Finger to finger.	Finger to nose.	Toe to finger.	Buttoning clothing.	Full arm movement.	Elbow.	Wrist.	Fingers.	Full leg movement.	Ankle.	Ankle and toes.
Normal	Normal	Normal	Normal	Clumsy	Slight	Marked	Marked	Marked	Moderate	Marked	Marked.
Normal	Normal	Normal	Normal	Normal	Normal	Normal	Slight	Marked	Normal	Normal	Slight.
Normal	Normal	Normal	Normal	Normal	Slight	Normal	Slight	Moderate	Normal	Slight	Normal.
Normal	Normal	Normal	Normal	Slight clumsiness	Slight	None	Marked	Marked	Moderate	Marked	Marked.
Disturbance in hands and toes	Normal	Normal	Normal	Normal	Slight	Slight	Slight	Slight	Normal	Moderate	Slight.
Normal	Normal	Normal	Normal	Normal	Normal	Normal	Marked	Moderate	Normal	Normal	Marked.
Normal	Normal	Normal	Normal	Normal	Slight	Normal	Marked	Moderate	Normal	Slight	Moderate.
Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal.
Normal	Slight disturbance	Normal	Normal	Normal	Normal	Normal	Marked	Marked	Normal	Normal	Slight.
Lost in three outer toes	Slight disturbance	Slight	Normal	Slightly clumsy	Normal	Marked	Marked	Marked	Normal	Not tested	Not tested.

TUBERCULOSIS (CONCEALED): A HITHERTO UNRECOGNIZED CLINICAL TYPE.

By George Douglas Head, B.S., M.D.,
MINNEAPOLIS, MINN.

Tuberculosis, like its great companion disease syphilis, may present itself in a variety of clinical pictures, some of them easy of recognition and well established as clinical types, others more obscure and difficult to interpret, and still others as yet unrecognized.

One of the peculiarities of the tubercle bacillus, shared in by the spirochete of syphilis and the bacillus of leprosy, is the tendency which it often manifests to invade its host without at first causing much constitutional or local reaction and without producing pronounced symptoms indicative of its presence. This reaction on the part of the organism to the tubercle bacillus is often expressed only in terms of a mild toxemia and not the recognized clinical types which have been so often emphasized and so often described, and which the profession has too often considered as a *sine qua non* in order that a diagnosis of tuberculosis shall be made.

Tubercle bacilli often multiply very slowly in the human body and establish a firm foothold only after a long series of years. The symptoms expressing a rapid and violent reaction against the infection namely, fever, chills, loss in weight, pain, sweats, cough, etc.—so commonly encountered in the more pronounced clinical pictures, are wanting in these individuals. So widespread is this slow-burning concealed type of tuberculosis, and so varied is its symptomatology, that the clinician should always be upon the lookout for it and never consider that an obscure case, exhibiting symptoms of nervous and physical exhaustion, has been thoroughly studied until he has excluded it.

The various symptomatic pictures built around clinically recognizable tuberculous infections in the lungs, pleura, peritoneum, adrenals, meninges, joints, etc., the manifestations of which have been so carefully described by medical writers, do not concern us in this paper. Our attention is focused upon a hitherto unrecognized class of tuberculous individuals exhibiting toxic symptoms without localizing focal evidence of the disease, persons as certainly infected as those of the recognized type. Mendelsohn in 826 deaths from accident and violence found 20 per cent. of the individuals with healed or active tuberculous lesions. Concealed tuberculosis is therefore a common pathological state. Do such persons have complaints or abnormal sensations not experienced by the normal individual? If so, what are they? Is the presence of the tubercle bacillus responsible for these symptoms, or do these persons go about in a state of apparent health unconscious of the smoldering fires burning within? These are pertinent questions for consideration, and yet almost no attention has been paid to the symptoms of persons harboring this form of the disease, and no one, so far as I know, has attempted to work out a symptom syndrome which will assist in identifying it.

I wish to emphasize this fact. The profession has trained itself to consider only those sick persons as having tuberculosis in whom there can be found objective focal evidence of the disease in some organ of the body, the lungs, peritoneum, pleura, kidneys, or elsewhere. If this evidence is wanting, even though the individual may show well-marked signs of an abnormal physical and nervous state, we have not been ready to admit that tuberculosis exists, and even if we do admit its existence, we have not been willing to consider the presence of the tubercle bacillus in the organism as an etiological factor in the production of the symptoms of which the patient complains. That is, the clinical picture presented by tuberculosis (concealed) in the silent areas of the body, mediastinal or postperitoneal lymph glands, lungs, pleura, peritoneum, pericardium, and elsewhere, where no local objective signs can be detected to indicate its presence, and where the individual shows only the evidence of the slow-burning fires of a tuberculin toxemia without the presence of symptoms and clinical signs expressive of the localizing ravages of the bacillus itself, is not recognized as a clinical entity.

The symptoms of nervous and physical exhaustion associated with recognizable tuberculosis have been long recognized and dwelt upon by all writers upon this subject; but that persons showing symptoms of nervous and physical exhaustion (toxic symptoms) and exhibiting no clinical evidence of tuberculosis could still be tuberculous, and that the quiescent, silent process could serve as the etiological factor, for the symptoms of physical and nervous exhaustion of which they complain has been overlooked. The profession has, therefore, gone on complacently stamping its brand of neurasthenia, asthenia, nervous exhaustion, psychasthenia, Glénard's disease, etc., upon those poor creatures, adults and children, in whom no organic cause could be detected to account for the symptoms of which they complain without attempting to determine whether a form of tuberculosis exists which exhibits no physical signs and which can only be detected by a specific (tuberculin) test.

The clinical conception of this type of tuberculosis I can best illustrate by the history of a case of lues which came under my observation some years ago.

The patient was a married woman, aged forty-five years, without children. She was well and strong up until her twenty-fifth year, when she began to develop a peculiar train of symptoms, interpreted by various physicians in this country and abroad as nervous exhaustion. She lost weight, became somewhat anemic, tired easily, had spells of faintness, and most peculiar attacks in which while walking upon the street or sitting conversing with friends or at the theatre she would suddenly feel as if a great dark cloud were descending over her, objects were seen and heard at a distance as though looked at through smoked glass. She would become dizzy, and if standing must sit down. After a few moments the attack would pass off. If she were walking upon the street and the attack came on she would support herself by leaning against a building or some near object. Years went by without relief. She became weak and prostrated; all mental and physical exertion tired her; her memory became poor; she expressed herself as good for nothing; living a vegetative existence; going about as in a dream; interested in no one. She lost weight, became depressed, and disheartened. One consultant after another examined her only to state that he could find nothing organic, and that she was suffering from nervous exhaustion.

A careful physical examination of this patient was negative for organic disease. Not a single recognizable symptom or sign of syphilis could be detected. She had a slight secondary anemia. The Wassermann reaction, which had not before been taken, was strongly positive. With this information the patient was questioned closely, and finally recalled that when a young woman, and while engaged to be married, a sore appeared upon her lip similar to one which had for sometime been upon the under lip of her fiancé. She had consulted a physician, who had given her medicine for her blood, and the sore had finally healed. She had never had other symptoms or signs of a luetic infection. Her physician had never told her the nature of the infection.

A diagnosis of syphilis was made. The patient was immediately placed upon specific treatment. The result of a year's treatment was marvelous. From a weak, nervous creature of no use to herself or anyone else she became a strong, energetic, active woman, the attacks of exhaustion, with dizziness and faintness, gone, memory restored, weight regained, able to fulfill her function in life, and interested in the affairs of her home and society.

Now here was a patient with lues, suffering from the infection, but without a single recognized symptom or physical sign suggestive of the disease in any organ or tissue of the body. Because of the lack of these symptoms and signs the various diagnoses of neurasthenia, psychasthenia, and nervous exhaustion had been made. It was syphilis without the focal signs of the disease. It was syphilis revealed by a specific test and not by clinical symptoms or physical signs. The patient was, however, as truly suffering from the disease as if she had had gummata in her liver or necrotic bone lesions.

Now it is in exactly this sense that we must view the clinical picture here proposed, expressing a symptom type of tuberculosis so hidden that it many times cannot be detected by any means except a specific test; persons complaining of symptoms of nervous and physical exhaustion over years, in whom an exhaustive examination failed to disclose the presence of tuberculosis, just as in the case of lues cited the examination failed to detect the signs of syphilis, and in whom the presence of a tuberculous infection was determined just as the presence of syphilis was determined in the case cited above by the use of a specific test.

The following case is an example of this form of tuberculous infection to which I refer:

Miss E. L., aged twenty-three years, single, living at home, admitted to St. Barnabas's Hospital October 14, 1913, complaining of backache, insomina, spells of depression, and attacks of indigestion. Her family history was negative. When a young girl she had a playmate who later developed and died of tuberculosis of the lungs. The patient herself has never been very strong even as a child. Her past history included a long series of illnesses of various sorts: curvature of the spine at five years of age, at first thought to be tuberculous, later considered hysterical; chorea at ten years of age; dysmenorrhea at fifteen years associated with fainting spells and exhaustion, often keeping her in bed for days at a time during her menstrual period; various abdominal operations performed at different times, terminating in hysterectomy in February, 1912; no cause given by the operating surgeon for the hysterectomy other than that it was considered best for the patient's general state of health. No pathological lesions found at operation.

The history of the patient's present complaints dates back over a number of years and includes a long series of symptoms of indigestion, abdominal pain, backache, insomnia, constipation, fermentative indigestion, attacks of mental depression, crying spells, dizziness, aching in the neck, headache, and eye ache. Patient stated that she never had a good appetite, that the daily routine of her life exhausted her, and year after year found her building up from one attack of exhaustion only to relapse into another. She had lived a semi-invalid existence. She had tried to work at various times, but always had to give up because she became so tired and exhausted. She had had a slight nervous cough at times, but had never coughed sputum. Many consultants had examined her lungs, but had found nothing. In the last year the patient had lost about fifteen pounds in weight. In order to improve her digestion, she had dieted to such an extent that she could scarcely eat solid food of any kind.

Patient was a tall, angular-looking girl. High cheek bones, long chest and abdomen. Throat and teeth negative. Marked tremor of the upper eyelids with the eyes closed. Increased knee-jerks. Pupils reacted to light and accommodation. No incoördination. Some tremor of the finger tips. No enlargement of the thyroid; no exophthalmos. She presented all the stigmata of a highly nervous girl. Hands, arms, and legs twitched during the examination. She seemed melancholy and depressed.

A careful physical examination of the patient, including a searching examination of the lungs, revealed no evidence of organic disease. There was a moderate gastroptosis, dislocated kidney on the right side, some tenderness over the abdominal aorta and along the lower spine. Urine and gastric examinations were negative. No occult blood in stools. Blood was negative except a slight secondary anemia; hemoglobin, 87 per cent. Wassermann reaction negative. Von Pirquet test positive.

Patient was studied in the hospital over a period of two weeks. She had occasional rises in temperature to 99.2°; pulse 85 to 100. No definite diagnosis could be made. She presented all the earmarks of a highly neurotic young woman suffering from nervous and physical exhaustion. She had frequent crying spells, much mental depression. She had occasional attacks of indigestion, was bothered much with insomnia, complained of cold hands and feet, backache, headache, and had a slight clearing of her throat. There was no sputum. On two different occasions she had fainting spells while going to the bathroom. Roentgen ray examinations of the spinal column and lungs negative.

The prolonged series of ailments and complaints dating back to girlhood, the symptoms of physical and nervous exhaustion, the absence of evidence of organic disease, seemed to justify the diagnosis of neurasthenia. But what kind of a diagnosis was neurasthenia? Why exclude syphilis in this case by a negative Wassermann reaction and fail to exclude tuberculosis by a tuberculin test?

On the fifteenth day after admission patient was given $\frac{1}{20}$ c.c. of a Bureau[1] tuberculin (5 mgms. of Koch's Old Tuberculin) and within sixteen hours exhibited a positive reaction, temperature going to 102°. Following the positive tuberculin test the clinical diagnosis of neurasthenia was abandoned and the diagnosis made of tuberculosis (concealed), focus not determined, with chronic tuberculous toxemia exhibiting symptoms of physical and nervous exhaustion.

Now here was a patient with tuberculosis but without a single recognized physical sign of the disease in any organ or tissue of the body. It was tuberculosis without the focal signs of the disease. It was tuberculosis without the well-known recognized symptoms of the disease. It was tuberculosis revealed by a specific test and not by clinical symptoms and physical signs. This patient was, however, as truly infected with the tubercle bacillus as if she had had a consolidated area in the apex of the right lung or tuberculous lymph glands of the neck. In the one case the location of the bacillus is known, in the other it is not known. Surely the failure to locate the lesion is no good reason for denying the diagnosis provided it rests upon good grounds.

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[1] This tuberculin is a 10 per cent. solution of Koch's Old Tuberculin, and is made by the Bureau of Animal Industry at Washington.

While it must be admitted that this individual is tuberculous and is negative for other organic disease, the evidence presented does not establish a casual relationship between the symptoms of physical and nervous exhaustion and the tuberculous process. "Is not the case presented really a patient with neurasthenia harboring an associated tuberculous process?" Such an interpretation of this case is unreasonable. If some one will demonstrate a pathological base for neurasthenia, so that it can be identified and differentiated from other diseases of known pathology the discussion upon this phase of the subject might be properly continued. In the absence of such lesions and with reliable proof of the existence in this person of a tuberculous process, and that only, it is only reasonable to conclude that the symptoms of which the patient complains is an expression of a disease (tuberculosis) which is common and about which we know a great deal, and which in its recognized forms often expresses in the highest degree symptoms of nervous and physical exhaustion, rather than a name, a symptom-complex, about which we know nothing.

But the question may be raised, "What pathological evidence can be offered to prove that a tuberculous lesion exists in this individual?" Pathological proof in this instance is impossible. Patients like this one are living. When they do die and are examined of what value is the evidence? If a tuberculous lesion were present at autopsy how could one know that it was there at the time the patient complained of her symptoms? If a tuberculous lesion were present and healed, how could one know that it was healed at the time of the patient's illness? If it were present and active, how could one know whether the lesion had been present and active at the time the patient complained of her nervous and physical exhaustion? Postmortem and clinical experience has proved the reliability and specificity of a positive subcutaneous test as proof of the existence of an active tuberculosis. Further evidence than this need not be carried into court in settling the question raised.

The diagnosis in this case, just as in the case of lues previously cited, rests upon a specific test. This in itself is the best evidence which can be offered to prove that the patient is harboring a tuberculous process.

In a previous paper[2] I presented a careful study of fifteen cases such as has been here described, all negative for other organic disease and all proved to be tuberculosis by an injection of tuberculin, and pictured this symptom type of quiescent or what I preferred to call "concealed tuberculosis" as follows:

"A person usually under twenty-five years of age, with, or sometimes without, a history of known exposure to tuberculosis, often dating back to childhood, comes complaining of a varied lot of symptoms expressing nervous and physical exhaustion, the most common of which are indigestion, headache, constipation, mental depression, cold hands and feet, backache, neckache, eyeache, voice tire, clearing of the throat, crying spells, chilliness, and loss of weight. These symptoms have dated back over a number of years with period of improvement followed by relapse under unusual nervous or physical strain. Partial or complete breakdown often results.

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[2] Jour. Am. Med. Assn., 1914, lxiii, 996.

On inspection one notes a poorly nourished, high-strung person with angular features, high cheek bones, long chest and abdomen, slender arms and legs, and active reflexes.

A careful physical examination reveals no positive evidence of organic disease. Enteroptosis is usually present. Normal or doubtful lung signs are usually encountered. The pulse-rate is, as a rule, increased, the temperature record may be normal or show an occasional afternoon rise to from 99.2° to 99.4° or more. The laboratory findings, including Wassermann test, are negative for organic disease. The roentgen-ray studies of the lungs for tuberculosis show positive, doubtful, or negative signs.

The long history of physical and nervous exhaustion with many relapses, the build and nervous construction of the individual, the absence of the signs of organic disease lead to the diagnosis of neurasthenia (so-called). The patient, however, usually gives a prompt von Pirquet test and always reacts positive to a subcutaneous injection of tuberculin."

This is a clinical type of tuberculosis which should be recognized. It is a clinical picture of tuberculous toxemia without the focal evidence of the disease. It is tuberculosis revealed by a specific test.

Persons with this symptom-complex are negative for organic lesions other than those produced by the tubercle bacillus. With such information before him, what intelligent physician would still cling to a diagnosis of so-called neurasthenia?

Most persons exhibiting symptoms of physical and nervous exhaustion harbor disease of one kind or another provided the examination has been thorough enough to disclose it. Whether the disease is of tuberculous, syphilitic, cardiac, nephritic, gastric, thyroiditic, hemic, or septic origin must be determined in each individual case. Some so-called neurasthenics in whom a most careful examination fails to detect organic disease other than tuberculosis do not react to a maximum dose of tuberculin given subcutaneously. The percentage of such cases is, however, small if the examination is thorough and a large series is studied. I am contending for the recognition by the profession of a symptom type of tuberculosis which is an expression of the silent concealed form of the infection, the symptom-complex of which corresponds with the at present accepted symptomatic clinical pictures built around so-called neurasthenia.

These cases are common. They can be recognized by a specific (tuberculin) test. They should be diagnosed and treated as tuberculosis and not as some form of nervous exhaustion.

ACUTE HEART BLOCK OCCURRING AS THE FIRST SIGN OF RHEUMATIC FEVER.

By Paul D. White, M.D.,
BOSTON.

(From the Medical Service of the Massachusetts General Hospital)

Acute heart block occurring in patients during the course of rheumatic fever has been reported by several writers, most recently by Christen Lundsgaard,[1] of Copenhagen, who mentions also other recorded cases, but the detection of an acute heart block prior to the finding of other signs of rheumatic fever infection is so unique and important as to deserve special mention. A patient has recently come under my observation who exhibited this condition. Of additional interest in this patient were the transient character of the block and the absence of any evidence of valve damage. In the case of transient heart block in rheumatic infection described by Lundsgaard,[2] in the case reported by Magnus-Alsleben,[3] in that of Cowan, M'Leod and Patterson,[4] and in three described by Mackenzie,[5] his cases Nos. 85, 87, and 88, there was no evidence of valve damage during the illness of the patient. In the patient described by Cowan, M'Leod and Patterson, a short soft systolic murmur was heard at the apex two months after the illness.

Case Report. A. J. B., aged eighteen years. Family and past history unimportant. Visited the out-patient department of the Massachusetts General Hospital December 16, 1915, because he ached "all over." Four days previously he had "caught cold," and since then he had had coryza, cough, headache, and backache. For a couple of days he had been bothered by palpitation, and for one day he had noticed lameness in his right arm, but he complained of no definite joint pain. No medicine had been taken.

Physical Examination. The boy appeared sick, but examination revealed nothing but redness of the throat (tonsils not large or inflamed), pronounced reduplication of the cardiac second sound heard best at the apex, and an irregularity of the pulse. The temperature was normal and the urine normal. The joints appeared normal. The seriousness of the lad's condition was not appreciated until the graphic record of the pulse was obtained.

A polygram of radial and jugular pulses (Fig. 1) showed very defective auriculoventricular conduction with marked prolongation of the *a–c* interval (up to 0.5 second), frequently leading up to dropped beats. In the venous tracing the *a* and *v* waves occur together, producing the very high excursions. Right or left vagal pressure increased readily the degree of block.

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[1] Lancet, London, 1916, cxc, 125.

[2] Loc. cit.

[3] Ztschr. f. klin. Med., 1910, lxix, 82.

[4] Quart. Jour. Med., 1910, iii, 115.

[5] Diseases of the Heart, London, 1913, 456.

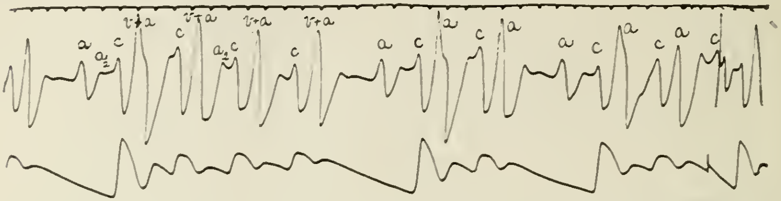

FIG. 1.—Polygram taken December 16, 1915, showing heart block with very long *a–c* interval (up to 0.5 second) and occasional dropped beats. Upper record is of jugular pulse, lower of radial pulse. Time interval = 0.2 second. This and subsequent tracings reduced to about ⅔ original size.

After establishment of this diagnosis of heart block, apparently of infectious origin, the patient went to bed, where he remained for the next two weeks, suffering from a severe attack of acute polyarticular rheumatism. The joint symptoms began a few hours

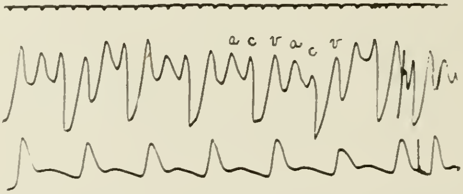

FIG. 2.—Polygram taken December 20, 1915, showing long *a–c* interval (0.3 second) but no dropped beats. Time interval = 0.2 second.

after the visit to the hospital, and in four days (December 20, 1915) the knees, toes, and right hand had all become involved with swelling, redness, pain, and tenderness. Treatment consisted of the administration of salicylates by mouth and of oil of gaultheria

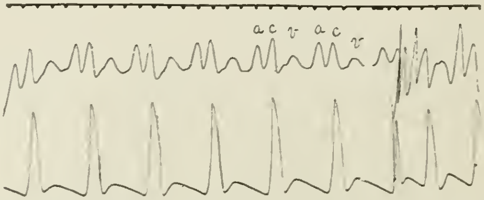

FIG. 3.—Polygram taken February 19, 1916, showing normal *a–c* interval (0.18 ± second). Time interval = 0.2 second.

applied to the affected joints. On December 20 a polygram (Fig. 2) showed no longer any dropped beats, but still a definite prolongation of the *a–c* interval.

On January 11, 1916, the patient again visited the out-patient department of the hospital and an electrocardiogram showed normal rhythm with a P–R interval slightly long (0.20 second). At this time he felt well except for slight pain in the left heel. No enlargement of the heart was made out and there were no murmurs. The reduplication of the second sound had disappeared. The joints appeared normal.

On January 29, forty-five days after the block was first discovered, an electrocardiogram showed normal rhythm with a perfectly normal P–R interval (0.145 second). At this time he felt well. On February 19, three weeks later, a polygram (Fig. 3) showed a normal *a–c* interval (0.18 second) and the patient felt well except for rare short sharp pains in his precordia during work which he had resumed. The work consisted of heavy lifting and lighter work was advised. Physical examination at this time showed the apex impulse 2 cm. inside the nipple line in the fifth and sixth intercostal spaces. There was no systolic retraction at the apex. No murmurs or reduplication were heard; the first sound was soft. $P2 > A2$ but not accentuated. Pulse rate = 72.

SUMMARY. A case is recorded in which acute and transient heart block appeared as the first sign of an acute rheumatic fever. The conduction time between auricle and ventricle showed great delay before the onset of the joint symptoms and returned to normal about six weeks after the block was discovered. In this case the myocardium not only gave the first evidence of the importance of the illness but also showed at least temporary damage while no evidence was found of endocardial or pericardial involvement.

The value of the graphic study of the pulse is well illustrated by this case.

REVIEWS

Blood-pressure: Its Clinical Applications. By George W. Norris, A.B., M.D., Assistant Professor of Medicine in the University of Pennsylvania; Assistant Visiting Physician, University Hospital. Second edition. Pp. 424; 133 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

The rapid exhaustion of the edition of a book does not necessarily show the inherent value of the book, as other factors, aside from the real worth of the work, may at times induce a ready sale. But this generalization does not apply to Dr. Norris's work which is now appearing in the second edition in a comparatively short time after the publication of the first. In this case it can be fairly stated that the first volume on blood-pressure was so complete and thorough, and so painstakingly prepared, that its wide-spread popularity was well merited. In this new edition Dr. Norris has incorporated much fresh material in the ever-changing and advancing study of vascular pressure. He has incorporated new researches, both clinical and laboratory, and in every way has kept abreast of his subject. There is one criticism, however, of the book which may be expressed. Dr. Norris is an authority on his subject, therefore it would enhance the value of his work were he to express more didactically his own opinions of the various methods and procedures which he discusses. In this way the less expert reader would have the definite opinion of one qualified to express, for example, which method is best in estimating the functional efficiency of the circulation. As it is now the book describes so many different methods that it is difficult to pick out the best one without guidance. J. H. M., Jr.

Rules for Recovery from Pulmonary Tuberculosis. A Layman's Hand-book of Treatment. By Lawrason Brown, M.D., of Saranac Lake, New York. Second edition. Pp. 184. Philadelphia and New York: Lea & Febiger, 1916.

Another edition of Dr. Brown's excellent little book of *Rules* is heartily welcome. Though seemingly a simple task, it required an expert to present the subject so briefly, so entertainingly, and so accurately. While such a book is in no sense intended as a substitute for the physician's instructions, it will in many instances be a valuable supplement to them. Besides directly applicable instruction, the book also contains much general information of a useful character about tuberculosis. It is to be hoped, however, that not only patients and other lay persons will profit by this volume, but that its valuable instructions will also be shared by physicians, medical students, and nurses. C. M. M.

DISEASES OF THE EYE: A HANDBOOK OF OPHTHALMIC PRACTICE FOR STUDENTS AND PRACTITIONERS. BY GEORGE E. DE SCHWEINITZ, M.D., LL.D. (Univ. of Pa.), Professor of Ophthalmology in the University of Pennsylvania; Ophthalmic Surgeon to the University Hospital; Consulting Ophthalmic Surgeon to Philadelphia Polyclinic Hospital, Philadelphia General Hospital, and Orthopedic Hospital and Infirmary for Nervous Diseases. Eighth edition. Pp. 754; 386 illustration and 7 colored plates. Philadelphia and London: W. B. Saunders Company, 1916.

WHEN a book passes through eight editions and a number of reprints in less than twenty-five years, on an average about one revision or reprint every second year, there is the best *prima facia* evidence that the work is one of real merit; and this is completely borne out by a perusal of the contents, however critical the reader may be. There is no exaggeration at all in declaring Dr. de Schweinitz's text-book to be the best of its kind in the English language, and unsurpassed in any other language. This is no slight praise, considering the high character of a number of books dealing with the same subject by other distinguished writers.

The subject-matter has been brought thoroughly up to date, although no epoch-making discoveries or improvements are to be chronicled in this domain since the last edition. We note that Lieutenant Colonel Elliot has written the description of the operation for glaucoma known by his name. The author observes of this method that he "is unconvinced that it is a better procedure than a technically correct iridectomy," while he regards it as a better operation in chronic non-congestive glaucoma than iridectomy and preferable to a second iridectomy or sclerotomy if a previous iridectomy has failed. He likewise is not very favorably impressed by Heine's operation of cyclodialysis as a substitute for iridectomy in ordinary acute or chronic glaucoma.

The typography, illustrations, paper, and general make-up of the volume are excellent and worthily represent the publishers' important contribution to a work of such merit. A full index completes the volume. T. B. S.

A Mechanistic View of War and Peace. By George W. Crile, M.D., Professor of Surgery, Western Reserve University. Pp. 104; 32 illustrations. New York: The Macmillan Company.

This small book will appeal to those who are familiar with Dr. Crile's other works and are in accord with his well-known theories. Although the book is in a sense descriptive of the present European war, yet it should not be read from this point of view but only as an interpretation of the phenomena of war upon the basis of the mechanistic theory. It is written from the view-point of this theory, in the terms peculiar to the theory, and upon one's belief in this theory, the value of the book will depend.

The quotation may help to make this clear. It is from the chapter entitled A Mechanistic View of German Kultur, p. 75: "A people may be brutalized into formal submission; but brutal treatment results in creating in the brains of the children the strongest action patterns of opposition and of hatred. The conquering enemy can never supplant the influence of the hating mother who plants action patterns in the brains of her children when the shades are drawn." O. H. P. P.

Medical Clinics of Chicago. Vol. 1, Nos. 5 and 6. Philadelphia and London: W. B. Saunders Company, 1916.

The fifth number of the *Medical Clinics* contains some very interesting and instructive case studies. Dr. Case contributes an article on roentgenological aspect of intestinal stasis. Dr. Williamson presents five different cases, of which the last one, showing the difficulty of distinguishing between carcinoma of the stomach and pernicious anemia, is most ably discussed. Dr. Preble has two cases which are interesting but marred by frequent questions and answers. Dr. Hamill discusses three neurological disorders. In Dr. Tice's clinics, in addition to the two cases that he shows, there is also a report on the autopsy of the case which was discussed in the January *Clinics*. Probably the most valuable and thorough of the different clinics is that of Dr. Abt, who has a splendid discussion on congential syphilis, which is illustrated by photographs and a colored plate. This number of the *Clinics* is concluded by the three cases of Dr. Mix.

The sixth number of the *Medical Clinics* contains, in addition to the authors in the previous number, also clinics of Dr. Hamburger, Dr. Tivnen, Dr. Friedman, and Dr. Zeisler. This number is uniformly good and contains some very interesting and valuable material. The clinics are all good, but it would be perfectly fair again to say that that of Dr. Abt is extremely carefully prepared and well illustrated. Dr. Hamburger also contributes a clinic which elaborates most carefully the present-day treatment of diabetes as advocated by Dr. Allen.

This last number of the *Medical Clinics of Chicago* shows a very distinct improvement over the earlier ones. There are still some things to which one takes exception, but, on the whole, they are a most novel and interesting method of learning at first hand the ideas and methods of men competent to discuss and to teach internal medicine. J. H. M., Jr.

The Starvation Treatment of Diabetes. By Lewis Webb Hill, M.D., Children's Hospital, Boston, and Rena S. Eckman, Dietitian, Massachusetts General Hospital, Boston. With an introduction by Richard C. Cabot, M.D. Second edition. Pp. 131. Boston: W. M. Leonard, 1916.

This small book on the details of the Allen treatment may be reviewed both accurately and comprehensively by quoting the last paragraph of the introduction written by Dr. Richard Cabot. "It is, of course, too early to say how far-reaching and how permanent the effects of such a diet will be in the severe and in the milder cases of diabetes. All we can say is that thus far it appears to work admirably well. To all who wish to give their patients the benefit of this treatment I can heartily recommend this book."

J. H. M., Jr.

Character and Temperament. By Joseph Jastrow, M.D. Pp. 596. New York and London: Appleton & Co.

This volume is the first of a series on general psychological subjects, the others being entitled, "The Qualities of Men," "The Subconscious," and "Fact and Fable in Psychology." One or two have been previously reviewed in this Journal. In all of these volumes, and especially in this, the effort is made to clearly present the subject of the psychological elements of the mind. The reviewer is not at all certain whether these volumes are meant for the student of psychology or if it is an effort to popularize the subject. It is difficult to adequately review a book of this kind because the subject is so large and the presentation so difficult. The reviewer who has taught medical students for many years would hardly recommend this book to students because the method of presentation is not attractive. The paragraphs are large, many of them an entire page, and some two, and while one may conceive that a student of psychology would be sufficiently interested to read paragraphs of this sort, yet is this the wisest way to present any subject? T. H. W.

A TEXT-BOOK OF HISTOLOGY. By RUDOLF KRAUSE, Professor of Anatomy at the University of Berlin. Pp. 274; 36 illustrations. New York: Rebman Company.

THIS appears to be intended as a companion book to Professor Krause's *A Course in Normal Histology*, published in 1913 and reviewed in AM. JOUR. MED. SC., May, 1914. This latter work was principally of the nature of an atlas of colored plates, with a descriptive account of each illustrated tissue or organ. The present work is a comprehensive text-book, illustrated for the most part with schematic explanatory figures. It is stated on the title-page that the references to illustrations given in the text relate to the colored illustrations in the previous larger work. Thus for a complete survey of the field of normal histology it would be necessary to have both books, as they are, in many ways, complementary to one another. One also learns from the title-page that this text was translated from an original manuscript and is now printed the first time. Considering this method of preparation the book is well done and only small errors of fact have been detected. But in the literal translation of some of the original names the writer has not always brought his terms into line with current nomenclature. This method of preparation has also its merits, for, no doubt, one gets a more vivid and interesting account of the subject when taken directly from the lecturer. Many more details of physiological chemistry are contained than usually given in current histologies, and, in many ways, the book represents an interesting exposition of the subject. W. H. F. A.

THE NEW PUBLIC HEALTH. By H. W. HILL, Professor of Public Health, Western University. Pp. 205. New York: The Macmillan Company, 1916.

IN the several chapters of this book the author clearly brings out his contention that the old public health was concerned with the environment; the new is concerned with the individual. The vastness of the problem of prevention of disease is thus made comparatively simple. For example, if instead of improving the environment of the 100,000,000 people in the United States we give proper supervision to the 200,000 people infected with tuberculosis the problem is but one five-hundredth the magnitude.

Very strong emphasis is made of the care of infective discharges. Indeed this seems probably the most important factor in the new public health. Thus we see that tuberculosis, pneumonia, and the other infectious diseases will develop under almost any circumstances if the dose of infection be large enough, virulent enough, or sufficiently repeated. These same diseases will not develop under any circumstances without such infection.

It is the belief of the author that mothers, because of intimate contact, propagate and keep alive and spread the infectious diseases of children more than any other one body of people. The basic principles of public health, therefore, should be taught in public schools in order to reach girls, the prospective mothers of the race.

The common fallacies and superstitions of a former generation, many of which are still believed in spite of their absurdity, are discussed in an interesting manner. The as yet unsolved problem of venereal prophylaxis is but lightly touched in this book.

The chapters are logically arranged, and each contains at the end a well-written summary. A. G. M.

An Index of Treatment. By Various Writers. Edited by Robert Hutchison, M.D., F.R.C.P., Physician to the London Hospital, and Physician (with Charge of Out-Patients) to the Hospital for Sick Children, and James Sherren, F.R.C.S., Surgeon to the London Hospital and Senior Surgeon to the Poplar Hospital for Accidents. Revised to conform with American usage by Warren Coleman, M.D., Professor of Clinical Medicine and Practical Pharmacology, Cornell University Medical College. Seventh edition. Pp., 1152; 82 illustrations. New York: William Wood & Co.

The purpose of this work is to furnish the general practitioner with a complete and trustworthy guide to modern methods of treatment, in a convenient form for reference.

The list of contributors consists of eighty-nine British authors, many of whom are of such prominence as to assure the success of any work undertaken by them; and this, coupled with the fact that it has run through seven editions, gives it a warm recommendation.

The authors have avoided any unnecessary presentation of a confusing number of procedures and have adhered throughout to the most effective and direct methods. There are no chapters, the book starting with the treatment of diseases in alphabetical order, this order being maintained throughout. The surgical articles are devoted more to non-operative treatment and to minor or emergency operations of the type the general practitioner might be called upon to perform, while the technic of the more elaborate operations is omitted as is the management of labor, the latter being conceded to be without the scope of this work.

The description of treatment is very similar to that found in text-books of medicine, surgery, and the various specialties, and includes procedures for practically every diseased condition regardless of the field into which it falls. The descriptions of necessity fall short of the completeness of a system on treatment, in places being rather sketchy, while in others, as the blood diseases and rheumatoid arthritis, they leave nothing to be desired.. The book is of unquestionable value to the general practitioner, who may encounter any of the conditions mentioned and who may not be fortunate enough to possess the various systems or the text-books of the specialties, which he as a practitioner may encounter.

The book is rather cumbersome in size, and the print is decidedly too small. Two volumes and larger print would be an advantage.

A. H. H.

TEXT-BOOK OF NERVOUS DISEASES. By CHARLES L. DANA, M.D. Eighth edition. Pp. 632; 262 illustrations. New York: William Wood & Co.

THIS is the eighth edition of this well-known work, the first being published twenty-three years ago. Comparing this with the previous edition there is the greatest difference, and it seems almost as if one is reading an entirely new work. There is little consideration given to anatomy, the author taking the position that in modern neurology any extensive discussion of anatomy is out of place, as special books are numerous on this subject. There is the usual treatment of symptoms, not much of a discussion on pathology and then the usual consideration of various clinical phases of nervous diseases beginning with peripheral nerves, then the cranial nerves, spinal-cord diseases, brain diseases, the various forms of functional disease, and finally the general diseases. There is a very interesting closing chapter on craniocerebral topography and an appendix in which is given the functional innervation of the muscles. The book is freely and well illustrated, although there is not as free a use of charts as there might be. It is needless to discuss the treatment of the subject matter, for any work by Dr. Dana is bound to be first class. No work ever reaches an eighth edition unless it is well worth while. T. H. W.

HOSPITALS AND THE LAW. By EDWIN VALENTINE MITCHELL, LL.B., of the Faculty of the College of Law, University of South Dakota. Pp. 178. New York: Rebman Company, 1915.

PROFESSIONAL literature grows so rapidly that it is becoming more and more impossible for one to keep in touch with even that of his own vocation; much less is it possible to know the literature of the other professions. Yet the activities of the various callings are so interrelated that every well-informed member of each must know something about the others. This is especially true as between the law and medicine. For most of us it can be accomplished only through summaries of the important and well-established facts bearing along the particular lines in which one is interested. Such a summary is this presentation of Dr. Mitchell's. He has brought together the essential legal practices in relation to hospitals and has so served to make possible for the physician and others an understanding of those practices without the necessity of a prolonged search in legal literature.

The book is well written, concise, sufficiently indexed, and gives references to rulings and decisions upon which its statements are based. It will be found most helpful to those interested in hospital management. T. G. M.

A Guide to Gynecology in General Practice. By Comyns Berkeley, M.A., M.D., M.C. (Cantab.), F.R.C.P. (Lond.), Obstetric and Gynecological Surgeon to the Middlesex Hospital and Surgeon-in-Charge of its Military Hospital at Clacton-on-Sea; Surgeon to the Chelsea Hospital for Women; Senior Obstetric Surgeon to the City of London Lying-in Hospital, etc., and Victor Bonney, M.S., M.D., B.Sc. (Lond.), F.R.C.S. (Eng.), M.R.C.P. (Lond.), Assistant Obstetric and Gynecological Surgeon to the Middlesex Hospital and Surgeon-in-Charge of its Military Hospital at Clacton-on-sea; Surgeon to the Chelsea Hospital for Women and the Hounslow Hospital, etc. London: Henry Frowde, Oxford University Press; Hodder & Stoughton, Warwick Square, E. C.

This volume is constructed along lines entirely different from those which we are accustomed to expect in text-books, since the sole aim of the authors has been to demonstrate the *significance* of symptoms and the *interpretation* of physical signs. To this end they have divided the book into five sections. In the first section the various methods of examination of patients and the more common instruments used in such examinations are briefly but clearly considered. The second section is devoted to the consideration of symptoms as such, each symptom being carefully considered in its relation to the various conditions in which it might be found, while disease entities are not considered *per se*. Thus, for example, a fibromyoma of the uterus is not described as a separate clinical condition, but is classified under various headings such as uterine hemorrhage, menstrual pain, sterility, etc. The third section of the book deals with physical signs in a similar manner, and it is this "cross-index" feature of the book that renders it of especial value to the practitioner and student. The treatment of the various conditions described form the fourth section of the book, but operative technic has been deliberately omitted. In this section many practical suggestions are offered, including the publication of prescriptions which the authors have found of service in their wide experience. A bit of conservatism is inferred concerning the value of radium in the treatment of carcinoma of the cervix, and it is surprising to note that early operation is recommended in gonorrheal salpingitis and that phylacogens are suggested in the treatment of chronic gonorrhea. The final section of the book is devoted to the medicolegal aspects of gynecology according to the laws of England, embracing such topics as nullity of marriage, rape, criminal abortion, foreign bodies left in the uterus, vagina, or abdomen, etc.

As a whole, the book is one which should be in the hands of every practitioner who attends gynecological cases, and the numerous semidiagrammatic illustrations and conciseness of the text should render the work especially appealing to the student. F. E. K.

Abdominal Injuries. By Prof. Rutherford Morison and Lieutenant-Colonel W. G. Richardson, R.A.M.C. (T.). Pp. 116; 16 illustrations. London: Oxford Medical Press.

The book is written by Rutherford Morison. Colonel Richardson's name appears by reason of the diagrams which are of little value. The author states that there is no essential difference between the surgical principles which should guide civil and military surgeons. The bulk of the volume is made up of a description of operative technic and postoperative complications and their treatment which differs essentially from the ordinary text-books. The subject of diagnosis is well presented. A few pages are devoted to general considerations of penetrating perforating and gunshot wounds. G. M. L.

Wounds in War. Their Treatment and Results. By Lieutenant-Colonel d'Arcy Power, R.A.M.C. Pp. 104. London: Oxford Medical Press.

The American surgeon who seeks the knowledge already gained by the combined experience of many military surgeons will be disappointed in this book. It is truly a "primer." The general principles of suppurating wounds in their various aspects are discussed with special reference to antiseptic methods, but the treatment of specific infections such as tetanus and gaseous gangrene is superficial and incomplete. G. M. L.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

Proteose Intoxication.—G. H. Whipple (*Jour. Am. Med. Assn.*, 1916, lxvii, 15) reports further findings in his study of proteose intoxication which develops in intestinal obstruction, general peritonitis and acute hemorrhage pancreatitis. He and his co-workers have demonstrated experimentally that the intoxication of intestinal obstruction is due to a primary proteose which may be precipitated by five volumes of 95 per cent. alcohol or by half saturation with ammonium sulphate. They have found that the proteose is resistant to digestion by intestinal mucosa and by pancreatic and tissue ferments. An animal injected with one proteose is found to be resistant not only to this proteose but also to other proteoses. The toxic proteoses isolated from the intestine from the peritoneum and from the pancreas have certain biologic reactions in common but give no specific differential reactions. Proteoses may be formed in the experimental animals independent of bacterial action. Cooke, Rodenbaugh and Whipple (*Jour. Exp. Med.*, 1916, xxiii, No. 6) have shown that there is a considerable rise in non-coagulable nitrogen in the blood in many conditions of intoxication, especially in acute intestinal obstruction. Without impairment of renal function, the non-coagulable nitrogen may increase from 25 mg. to 100 or 200 mg. per 100 c.c. of blood. Acute proteose intoxications due to the injection of a pure proteose into a normal dog may show a rise in non-coagulable nitrogen in the blood from 25 mg. to 40 or 60 mg. within three or four hours. To throw light on this observation, dogs have been kept in metabolism cages during starvation until the elimination of urinary nitrogen has become constant (usually four or five days). If, now, a small dose of pure proteose is given intravenously, there will be a great increase in the urinary nitrogen excretion (100 per cent. or more), which may last three to five days. It seems clear that this nitrogen increase must result from tissue catabolism. Animals kept in the same way also show a great rise in the nitrogen elimination if a closed loop of intestine is produced. The authors have produced "a certain type of simple duodenal obstruction" with which there is little or no vomiting and no dehydration. In such cases animals may show over 200 per cent. increase in urinary nitrogen, and death in six to eight days, with a blood non-coagulable nitrogen well over 100 mg. per 100 c.c. Results quite similar to those in intestinal obstruction have been obtained in general peritonitis both septic and sterile, and in acute hemorrhagic pancreatitis, showing that there is a definite proteose intoxication in these conditions.

A Cause of Ascites.—C. F. Hoover (*Jour. Am. Med. Assn.*, 1916, lxviii, 12) reports some clinical observations which are of interest in connection with the development of ascites. As the author points out, the cirrhotic changes in the liver itself are insufficient to explain the development of ascites, for cirrhosis of extreme grade may be present without accumulation of fluid in the peritoneal cavity. Again, it happens rather infrequently that a patient with cirrhosis of the liver will develop ascites, which may subsequently disappear for months or longer. Recently, Hoover had under observation a patient with alcoholic cirrhosis of the liver. Three weeks before admission to the hospital he had complained of swelling of the feet, legs and abdomen. He stopped work and quit drinking alcoholics, and the swellings disappeared, whereupon he resumed both work and drinking. The swellings again returned and he became jaundiced. The patient had a firm, enlarged liver. There was a caput medusæ over which there was a palpable thrill and a loud venous hum. Systolic blood-pressure was 130, diastolic 90. Eight liters of clear yellow serous fluid were removed. Its specific gravity was 1.005, albumin 4.5 gms. per liter and cell count 180 per 1 cmm. Within a few days, the patient began to improve, the jaundice diminished, and the swelling of the liver subsided. With these changes in the patients condition, there was no alteration in the systolic and diastolic blood-pressures and no visible change in the caput medusæ. It was found, however, that the venous thrill and the murmur had disappeared, a fact which the author ascribes to a lowering of the portal pressure, coincidental with decrease in size of the liver. The findings in this case, together with other clinical observations, lead the author to believe that swelling of the liver is a cause of elevation of portal pressure and that increase of portal pressure is an important factor in the development of ascites of hepatic origin.

On the Reaction of the Cerebrospinal Fluid.—S. H. Hurwitz and C. L. Tranter (*Arch. Int. Med.*, 1916, xvii (Part I), 828) have made a study of the reaction of the cerebrospinal fluid, as determined by the colorimetric method of Levy, Rowntree and Marriott. The technic for the application of this method to the spinal fluid directly is given. The technic is so simple that the authors consider it applicable as a coutine procedure in examinations of cerebrospinal fluids. The authors summarize their findings as follows: As determined colorimetrically, normal cerebrospinal fluid is more alkaline than blood, the difference in the hydrogen ion concentration of the dialysates of the two fluids being equal to 0.45, the value of pH for cerebrospinal fluid being 8.11; value of pH for blood, 7.66. No alteration from the normal reaction has been noted either in the blood or in the fluid of patients suffering from primary or secondary syphilis or from syphilitic affections of the nervous system. Thus far, no study has been made of the reaction of the cerebrospinal fluid in acute inflammatory conditions of the meninges.

The Etiology of the Diseases of the Circulatory System.—Janeway (*Boston Med. and Surg. Jour.*, 1916, clxxiv, 925) has attempted, in this article, to advance our knowledge of the ultimate and contributory causes of diseases of the circulatory system, with the aim of stimulating wide-spread efforts to reduce their prevalence, for reliable figures, brought forward especially by Bouldan, show a definitely increasing incidence of diseases of the heart, arteries, and kidneys. The author has been able to draw certain logical conclusions as the result of his analysis primarily of the etiological factors concerned in cardiovascular disease. Eleven etiological categories are presented as follows: (1) Diseases due to known bacterial infections; (2) probable, but improved bacterial infections; (3) syphilis; (4) rare infections; (5) parasites and tumors; (6) intoxications; (7) nutritional disturbances; (8) mechanical disorders; (9) nervous disorders; (10) developmental defects; (11) hereditary disease. The author leaves little doubt as to the possibility of reducing the mortality from circulatory diseases. The measures, in order of their importance, best calculated to secure the result, are: (1) A reduction in the incidence of syphilis in association with better diagnosis for and more intensive treatment in the primary stage; (2) reduction of preventable infectious diseases; (3) public education to regard "rheumatism" as a serious malady to be seriously treated, even in mild cases, by the medical profession. In addition to these, Janeway further suggests the establishment of convalescent hospitals for the protracted care of cardiac cases, combined with the development of employments adapted to the limitations of various types of cardiac cases, the promotion in general of good hygiene, temperance, and the periodic medical examination of the presumably healthy. "The need of the moment, therefore, is for more knowledge; not more knowledge of the dangers of circulatory diseases for the public which means propaganda, but more knowledge of their causes for the physician, which means ceaseless investigation."

A Case of Acute Hodgkin's Disease.—Whittington (*Quart. Jour. Med.*, 1916, ix, 83) presents a case most interesting, by reason of the peculiar course and many difficulties in establishing a diagnosis, which was made certain only by autopsy. The striking features in the case are noted as follows: (1) The onset was acute and with signs and symptoms most suggestive of peritonitis. (2) The patient subsequently suggested typhoid fever with low delirium, apathy, dicrotic pulse, diarrhea, leukopenia, and splenic enlargement. (3) There was a curious periodicity not merely of the fever but of the signs and symptoms as well. Each period of fever marked the initiation of emaciation, rapidly developing pallor, and progressive splenic enlargement; during each afebrile period the spleen seemed to shrink. (4) There were pronounced signs of portal obstruction. (5) There was no enlargement of the external glands. (6) The blood showed a chlorotic anemia, a leukopenia of 3000, and no eosinophilia. On section the spleen was found much enlarged, as well as the retroperitoneal, portal, and thoracic glands. Histologically these showed the typical appearance of Hodgkin's disease, though the degree of connective-tissue proliferation was not far advanced. This fact and the occurrence of hemorrhagic areas in the glands fits in with the acutely fatal course of the disease. The whole case seems strongly to support the view that Hodgkin's disease is due to some infectious organism, at times much more virulent than at others.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

A Simple Technic for Intravenous Injections in Infants.—Martin (*Brit. Med. Jour.*, July 8, 1916, p. 40) says that on account of the small size and inaccessibility of the superficial veins in young infants, it is usually difficult, and often impossible, to give intravenous injections or even to obtain sufficient blood for the Wassermann reaction by the methods ordinarily employed. The difficulty is satisfactorily overcome by puncturing the superior longitudinal sinus through the anterior fontanelle, according to the procedure of Helmholtz. The following technic of the method is based on a series of 50 cases: The scalp over the anterior fontanelle is shaved and disinfected with iodine. No anesthetic is required. The child lies in bed with its head raised to a convenient angle on two pillows. A nurse holds the head securely with a hand on either side; the operator stands in front and on the right side of the child. The needle (held at an angle of about 50 to 60 degrees with the plane of the fontanelle) is inserted in the median line, half-way between the anterior angle and centre of the fontanelle. Some little force is required to push it through the firm pericranium, and when the resistance is overcome, one can feel that the point of the needle is in a cavity. The point should not penetrate more than one-eighth of an inch below the surface of the skin since the sinus lies immediately under the pericranium. If the needle is in the sinus blood flows at once into the syringe; should this not happen the needle has gone too deep, and has passed completely through the sinus. This is the mistake usually made by a beginner; it does not, however, cause any damage. The sinus is in many cases so shallow that an ordinary long pointed needle pierces the inner wall before the entire opening in the end of the needle is through the pericranium. A needle of size No. 20 or therabouts, with a bevel measuring 2 mm., should be chosen in place of one with an ordinary bevel, which measures about 4.5 mm. Autopsies on patients in whom, for diagnostic of therapeutic purposes, the sinus has been punctured at intervals of from a few hours to several weeks before death, showed that in no case had any injury been done, nor in any case in which this method has been used have any untoward symptom followed.

Death After Nitrous Oxide-Oxygen Anesthesia.—McCardie (*Brit. Med. Jour.*, July 22, 1916, p. 109) says that in a somewhat large experience of nitrous oxide and oxygen anesthesia, with and without the addition of ether, he has never seen any other case like this one. The patient very nearly died during the operation and succumbed two hours and a half later without recovering consciousness. The operation, gastro-enterostomy for simple ulcer, was done in a thin, anemic, nervous man, aged sixty-six years, who was considered to be a good subject for nitrous oxide and oxygen anesthesia. The anesthesia lasted thirty-five minutes during the last fifteen of which hardly any gas was given but a good deal of air, and a large quantity of oxygen with rebreathing. There was no respiratory obstruction at any time. McCardie suggests the following points for consideration: That the circulation failed long before respiration. The failure could not have been due to traumatic shock, because it began before incision. The morphine could not be incriminated, because the patient had had as big or bigger doses before, and was not drowsy before operation. There was no asphyxia from obstruction to respiration and twice as much oxygen as is usually necessary was inhaled, while very little gas was given. McCardie does not think that death was due to too much gas, because circulatory failure occurred very early, beginning with the administration of the gas. The patient was psychically a very curiously nervous man, and McCardie thinks that psychic shock, together with anemia, causing heart weakness were largely responsible for the fatality. He admits, however, that this explanation is hardly satisfactory.

The Treatment of Hemorrhoids by Interstitial Injection.—Bird (*Lancet*, July 22, 1916, p. 149) says that some years ago, he chose this treatment for hemorrhoids in himself for the following reasons: The prospect of complete relief in eight or nine visits, each taking a quarter of an hour; very slight pain of no duration; and at the same time no interference with his ordinary work and life. The only change that he noticed in the parts treated was an appreciable, but very slight, warmth. He is still perfectly comfortable. Pure carbolic acid as an injection into pile tissue was first used in the United States about half a century ago, but through misuse the practice fell into abeyance. Some thirty years ago it was resumed in a mitigated form by Dr. Hoyt, of New York. The deviations from his treatment in many hands seemed to have caused disappointment, perhaps through seeking more rapid or more complete success. There is no stretching of the sphincter and no confinement to bed. The solution for injection consists of equal parts of hazeline and distilled water, to which is added 10 per cent. of pure carbolic acid; the whole of the acid is not dissolved unless warmed; the bottle must be shaken when the solution becomes turbid from the finely disseminated acid, and is then ready for use. It should not be allowed to run on mucous membrane or skin, as in both cases it gives rise to soreness. Bird has had no trouble with carbolic acid absorption, though he has injected as much as 15 mm. at one sitting. The treatment has, at least, two disadvantages: the number of visits, and the passage of the anal speculum. He has found the best speculum to be Kelly's sphincteroscope, both for the first examination and the ensuing treatment, but it should always be well warmed before insertion and well lubricated. He has had made for himself a self-retaining speculum, as Kelly's requires one hand to retain it during the injection by the other. It is better not to inject a pile near the junction of the mucous membrane and the skin or external to that line before the inner or upper portions have been treated. External piles (inflamed) should be allowed to subside under appropriate treatment before injection and the patient should be advised against taking wine, spirits, and highly seasoned dishes and should be given medicines to produce soft evacuations. A platino-iridium needle not too fine and about an inch and a quarter long is perhaps the best, though he uses a short, stiff, needle on a prolongation that fits on to the Record syringe, as this gives a clear view of the length of the speculum. Care should be taken to keep the needle in the long axis of the bowel and a slight side-to-side motion as the plunger is pressed on tears the interior of the pile, and if the needle is kept in for a few seconds there is seldom any bleeding. After an injection or two the pile surface becomes hard, so that future injections should be made between the old scars until the pile is completely cured. An ordinary pile condition requires eight or ten injections, a commencing pile only one or two. At the first visit, Bird now gives preference to injections of not more than three minims superficially to different parts of the surface of the pile; this makes subsequent injections almost painless and prevents the swelling caused by larger injections made more deeply. Cases with two-day intervals between injections do better than those with longer intervals.

Separation of the Lower Femoral Epiphyseal.—MacAusland (*Surg., Gynec. and Obst.*, 1916, xxiii, 147) reports two of these rare cases and a statistical collection of thirty-six cases collected from the literature. This type of fracture usually occurs from direct violence, such as the catching of a leg in the spokes of a revolving wheel. The deformity is usually a displacement of the epiphysis backward into the popliteal space, the lower end of the shaft projecting its sharp edge forward above the patella. Conservative treatment of such displacement by the inclined plane, or other traction and splinting are useless. Closed reduction under an anesthetic is accompanied by dangers, injury to the popliteal vessels and nerves, and the improbability of obtaining complete reduction. The open reduction is necessary and is not only simple, but should always succeed in giving proper alignment and a clean blood-free joint. The details of operative procedure are as follows: A tourniquet is applied. A lateral incision, usually on the inner side, is carried down to the seat of fracture by blunt dissection, and the accumulated blood-clot thoroughly washed out. With a blunt dissector or other heavy instrument, the lower fragment is pried into place, usually without much resistance and usually with complete anatomical reduction of fragments. The well-fitted serrations give to the reduction a valued stability and as well insure against the slightest possible injury to the epiphysis. After closure of the wound and removal of the tourniquet, a plaster cast is applied from the groin to the ankle. At the end of one week the plaster is split and a few degrees of motion made without removal of the leg from the posterior shell. This process is repeated gently each day. The plaster is taken off after ten days, and from this time on there may be expected an uneventful convalescence.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

Epilepsy, with Special Reference to Treatment.—Dercum (*Jour. Am. Med. Assn.*, 1916, lxvii, 247) says that the first indication in the treatment of epilepsy is that the patient, though defective and deviate, should lead as physiological a life as is compatible. To attain this end a life without physical or mental strain, close to nature, in camp or on the farm, should be adopted by the epileptic. This, indeed, is the principle applied in the various epileptic colonies. In a given number of cases it is attended by an improvement in general health and a notable diminution in the number of seizures. There can be no doubt that the benefit is largely due to the increased oxidation of waste and toxic substances and the general increase of physiological efficiency which result from an outdoor life. In addition three points should be borne in mind: The diet should be so modified that in this organism, already toxic, as little strain as possible be placed on the liver, the thyroid, and other defensive glands. For this reason the red meats are to be partaken of sparingly. The carbohydrates also are to be diminished. To take the latter in large amount is to hamper the oxidation of the tissues, an oxidation which for the obvious reason of the autotoxicity of the patient should be maintained at as high a level as possible. In the diet, emphasis should be laid on the white meats, the succulent vegetables, and milk; eggs also may be permitted. Stimulants of all kinds are, of course, to be excluded. The various avenues of elimination should be kept freely open. If the diet does not of itself counteract the constipation frequently present, a moderate dose of a simple saline or laxative water may be given daily. The patient should drink water freely between meals to promote the action of the kidneys, and should take a luke-warm sponge bath daily to promote the action of the skin. The bath should not be such as to promote an active reaction, but merely to favor elimination. Resort to medicine must, of course, be had in many cases to influence or control the seizures. Time will not permit the extended discussion of these, but after all is said and done, experience teaches that chief reliance must be placed on the bromides. Regarding their efficient administration, however, one important point must be borne in mind, namely, the principle of sodium chloride withdrawal introduced by Richet and Toulouse. If table salt is withheld, the bromides instead of being eliminated are retained, and are effective in much smaller dose. Dercum has been in the habit, for many years past, of administering the bromides in the form of sodium bromide, at the same time instituting as rigid a withdrawal of the sodium chloride as possible. There can be no doubt that under these circumstances the sodium bromide takes the place, in a measure, of the sodium chloride in the tissues. If in a case so treated the sodium bromide be discontinued and sodium chloride resumed, the bromide is rapidly eliminated in the urine. But one other point of importance remains. In a given number of instances the physiological level of the patient may be distinctly raised by the administration, from time to time, of small doses of thyroid extract; from an eighth to a quarter of a grain, three times daily, seldom more. Thyroid in small doses, long continued, stimulates the chain of glands of internal secretion, increases oxidation, and promotes metabolism generally.

Studies on a Case of Bichloride Poisoning.—Lewis and Rivers (*Johns Hopkins Hosp. Bull.*, 1916, xxvii, 193) say that the necessity of prolonged and vigorous treatment of every case of bichloride poisoning cannot be too strongly emphasized. Many apparently moribund individuals have been saved by properly directed and vigorously pushed therapeutic measures. Death should be the only indication for a discontinuance of treatment prior to the complete recovery of the patient. Retention of waste nitrogen is undoubtedly a factor in the early fatal issue of these cases. There are rarely any signs of uremia. The protein sparing powers of the carbohydrates are of the greatest value in delaying the appearance of the extreme grades of nitrogen retention which usually precede death. If carbohydrates cannot be retained by mouth, glucose may be given intravenously in a 10 to 50 per cent. solution. In addition to its protein sparing action the glucose itself acts as a mild diuretic. It is probable that alkalis have a decidedly beneficial action. Macnider has recently pointed out that they are capable of protecting the kidneys from the full effects of uranium intoxication. It is possible that large doses of sodium bicarbonate given intravenously soon after the taking of the poison would exert a similar protective action in bichloride poisoning.

The Treatment of Paralysis Agitans with the Parathyroid Gland.—Berkeley (*Med. Record*, 1916, xc, 105) says that further experience seems to justify the opinion that the administration of the parathyroid glands does not assure a "cure" for paralysis agitans, but asserts that from 60 to 70 per cent. of the patients treated by this remedy have been greatly benefited, and that in such patients the progress of the disease has been arrested or very materially retarded. The author believes that much the best preparation of the parathyroid gland is an acetic acid extract of the fresh glands (commonly, though very inaccurately, called a "nucleoproteid" extract) made by treating the ground or triturated glands with cold distilled water, filtering, and then precipitating with very minute amounts of acetic acid. This extract is now prepared commercially, and may be obtained without great expense. Berkeley uses this extract in doses of one-fortieth of a grain either by mouth in a capsule with milk-sugar or hypodermically in a solution. The solution is given in doses of 15 minims, and, if it is injected with reasonable care, produces no local effects of a disagreeable nature. The article by Berkeley is not entirely convincing but very enthusiastic about the success of the parathyroid treatment in "hundreds of cases."

Arsenobenzol in the Treatment of Syphilis.—Ormsby and Mitchell (*Jour. Amer. Med. Assn.*, 1916, lxvi, 867) write concerning arsenobenzol which is an arsenic preparation manufactured in America as a substitute for salvarsan. The authors gave 184 injections to 75 patients suffering from syphilis in its various stages and believe that some conclusions as to the value of this remedy can be drawn. Its action has been uniform, its toxicity low, and its therapeutic results have been excellent. The immediate reactions have been almost negligible, and remote untoward results entirely absent. They employed it in both early and late cases, including those with primary lesions before eruptive manifestations have occurred; in the so-called secondary and tertiary stages; also in latent cases, and those involving the cerebro-spinal system. The authors give the detailed method of the preparation of the solution of the drug for intravenous injections. The preparation of the solution and the intravenous administration are very similar to that of salvarsan. In their conclusions Ormsby and Mitchell state that arsenobenzol, together with mercury, offers as good a method of treatment of syphilis as any heretofore used. In its uniform and non-toxic action, arsenobenzol commends itself as a remedial agent of great value in the treatment of syphilis, and its successful preparation marks an achievement in American chemotherapy. While a sufficient experience has not as yet been had from which to draw ultimate conclusions, they believe its therapeutic accomplishments, together with its safety of administration, recommend its continued employment.

The Reactions and Results of Treatment in Cerebrospinal Syphilis.—Draper (*Jour. Amer. Med. Assn.*, 1916, lxvi, 400) has made observations on 38 cases, watched over periods of from three months to three years. These 38 patients were given 1126 intravenous injections and 355 intraspinal injections of medicated serum. The technic of administration was the usual one. He found that the severest reaction to intravenous injections was of the anaphylactic type. The most frequent reaction to the intraspinal injections was pain. The severest was an aseptic meningitis, which might have been anaphylactic in origin. Twenty-six patients out of the total of 38 were economically useless before treatment. After treatment 22 were back on full time work. The rapidity and degree of improvement depended directly on the intensity of the treatment. Draper emphasizes the importance of keeping the patients at work on part time at least during the months of treatment in order that their period of disability may be shortened.

The Treatment of Pneumonia with Ethylhydrocuprein (Optochin).—Loeb (*Berlin. klin. Wchnschr.*, 1915, lii, 1108) reports his results in the treatment of pneumonia with optochin. He believes that the remedy, to be effective, should be given early, as soon as chill, fever, pains in chest and cough have appeared without waiting to make the diagnosis certain. The effect of the remedy is seen principally in a critical fall of the temperature usually on the day following its administration. The crisis may be a true one but as a rule there is a return of the fever and it is necessary to repeat the remedy. The results reported are favorable. Occasionally toxic symptoms resembling those due to overaction of quinine are produced by optochin, but these symptoms disappear promptly if the remedy is withdrawn for twelve to twenty-four hours.

The Local Treatment of Meningeal Syphilis.—Zennerich (*München. med. Wchnschr.*, 1915, lxii, 1696) sees no especial advantage in intraspinal administration of salvarsanized serum as compared to injections of small doses of salvarsan itself. He does not state this as a proved fact as he says that later and more complete reports may modify this view. In the term meningeal syphilis Zennerich includes cerebrospinal syphilis and also metaluetic infections. He emphasizes that treatment must be begun early in these syphilitic affections in order to secure results. He does not believe that the ordinary combined treatment, salvarsan and mercury, as applied to constitutional syphilis can exert any influence on meningeal syphilis. Intraspinal injection of salvarsan must be given with great caution, for too concentrated solutions may cause an increase in symptoms and may even produce a myelitis.

Strontium Salicylate.—Blankenhorn (*Jour. Amer. Med. Assn.*, 1916, lxvi, 331) says that salicylate of strontium has had a therapeutic reputation for which there is no satisfactory foundation discoverable. The chief advantage claimed for strontium salicylate as compared with sodium salicylate is that the strontium salt gives rise to fewer unpleasant by-effects, particularly digestive. The author endeavored to determine if strontium salicylate differed from sodium salicylate either as regards therapeutic efficiency or undesirable by-effects. The drug was easily given in all cases, and no more than the usual protest was made about the taste. Strontium salicylate is only slightly soluble in water and hence must be given in powder form which is less convenient and less accurate than the use of a stock solution of sodium salicylate. He found that strontium salicylate in comparable doses produced the same gastric and other toxic symptoms produced by other salicylates. No difference in therapeutic efficiency was observed. The fact that strontium salicylate is much more expensive and more inconvenient to give than sodium salicylate also helps to destroy the tradition held by some that this form of salicylate is superior to the more common sodium salt.

The Treatment of Paresis and Tabes Dorsalis by Salvarsanized Serum.—Cotton (*Amer. Jour. Insanity*, 1915, and 1916, lxxii, 125, 355, 485), in this article which is continued through three numbers of the above journal discusses the various methods that have been advocated for the treatment of tabes and paresis. The article includes interesting detailed case reports and tabulation of the results in the individual cases, for which the original article should be consulted. With regard to various methods of treatment Cotton considers from his experience that the Swift-Ellis method is as efficacious as any. The criticism of this method is that it has to be administered too slowly because of the dangers of too frequent intravenous injections of salvarsan. Treatment is thus extended over a considerable period of time before permanent results can be obtained. Consequently Cotton says that he has been combining the Swift-Ellis and Ogilvie methods on alternate weeks with good results. The author believes that the value of mercury and iodide of potassium as an adjunct to salvarsanized serum in the treatment of paresis and tabes is at present an unsettled question. With regard to the use of salvarsan or neosalvarsan there is also considerable difference of opinion. At first Cotton used neosalvarsan exclusively. The general opinion seemed to be in favor of salvarsan, and so the author has used salvarsan during the past nine months. His results were no better than with the neosalvarsan, and in two cases he had a pronounced aseptic meningitis with salvarsan, an experience which never occurred with the use of neosalvarsan. The total number of cases of paresis reported by Cotton was 66 and in all 600 treatments were given. From this number the author selected 31 patients for detailed study who were treated for at least six months, but in all but a very few cases the treatment extended for over two years or the patients have been observed for that length of time. Of this group of 31 patients, 11, or 35.5 per cent. are classified as arrested; 7, or 22.5 per cent. were much improved; 7, or 22.5 per cent. were not improved, and 6, or 19.5 per cent. died. Only 4 cases of tabes are reported occurring in patients from forty-eight to seventy years of age, and no especial conclusions can be drawn from these patients. For his conclusions Cotton emphasizes the fact that in the use of salvarsanized serum we have an agent which does cause definite arrest in paresis, which arrest includes improvement in the clinical symptoms, physical signs and a corresponding change in the biological reactions from positive to negative. To be effective the case must be treated in the early stages, as advanced stages show no favorable reaction to the treatment. The length of time is not always an indication of the severity of the symptoms, but the majority of cases cannot be helped after two or three years have elapsed. Treatment must be persistent and uninterrupted, grading the amount of dose and frequency of treatment to the condition of the patient. Taboparesis should be cautiously treated, usually with small doses and not oftener than every three weeks. The remissions caused by the treatment cannot be compared to spontaneous remission, for the percentage in the former is 35.5 per cent., and in the latter case only 4 per cent. The change in the cell count, globulin content, blood and spinal fluid Wassermann reactions are the direct result of the treatment and not to be compared with the variation found in untreated cases of paresis. The efficacy of the treatment depends not on the method used but on the stage of the disease; hence the necessity for early diagnosis in paresis and prompt treatment as soon as possible.

A Contribution to the Chemotherapy of Tuberculosis.—Koga (*Jour. Exper. Med.*, 1916, xxiv, 107) writes concerning a preparation of copper and potassium cyanid since named cyanocuprol. The preparation used by Koga is a double salt of copper and potassium cyanid diluted 1 to 2000 and treated in a special manner to prevent the formation of free hydrogen cyanid. He does not state what this special manipulation is, but insists that unless this manipulation is carried out, the injection of the remedy is not safe for human beings. Koga's contribution is divided into two papers. The first deals with the effect of the new remedy in animal experiments, in which over 150 guinea-pigs were used. In his summary of the effect of cyanocuprol in his animal experiments, he says that judging from the macroscopic and microscopic study of the animals its action seems to be about as follows: The effect of a single injection upon the lesions is either negative or inconspicuous. But after rejected injections of the preparation the congestion and leukocytic infiltration about the lesions are markedly decreased, the cheesy material resulting from degeneration of the lesions and other degenerative products are in process of absorption, and young connective tissue is being actively produced in the periphery. While these changes are taking place the number of the bacilli is also being reduced until finally they can no longer be found on microscopic examination. However, the complete disappearance of tubercle bacilli was disproved in some of the animals apparently cured by the treatment. Emulsions were made of the lungs, liver, spleen and other organs of some of the animals, apparently healed, and injected into the peritoneal cavity of guinea-pigs. Such injections were followed in some instances by the development of tuberculosis. Koga's experimental work is supplemented by a clinical report of sixty-three cases of human tuberculosis in various stages treated by the new remedy. Eleven of these cases are reported in detail. The author's conclusions, which seem to be justified by the reports, are "that the preparation greatly improves or apparently cures pulmonary tuberculosis and surgical tuberculosis in the first and second stages, and that it seems also to produce beneficial effects upon the disease in the third stage. The duration of these beneficial effects is still to be established by more numerous trials and many years of observation. The preparation must be given intravenously, and the doses must be increased or decreased according to the age and constitution of each patient. Moreover, it should be borne in mind that the pathological phenomena and the constitution of each patient have much to do with the determination of the dose. The manner of action of the preparation is not yet entirely clear. But if it acts primarily upon the tissues which bear the tubercular lesions and then indirectly against the germ, as he assumes at present, the activity which the tissues exert will have much to do with the efficacy of the preparation. If this hypothesis is correct, according to Koga, the minimum doses (10–12 mg.) will be best suited to a patient who is greatly emaciated, and should be gradually increased as the reactions, pathological processes, nutrition, etc., indicate. In any case, the dose of the preparation must be determined by the condition and constitution of the patient. In animal experiments he says that he has been fortunate enough to obtain results which no other preparation has given. The clinical application and the establishment of its full efficacy in human cases must be left to the physician.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Transperitoneal Celiohysterotomy.—Polak (*Am. Jour. Obst.*, July, 1916), has performed eight operations by the following method: Incision is six inches long at the right of the median line, below the umbilicus. The peritoneum is opened, the uterus pushed into the wound, the bladder and visceral peritoneum separated, and the peritoneal reflection of the uterus and that of the abdominal wall and the visceral and parietal layers are united by sutures. An interrupted figure-of-eight with catgut, leaving the ends long, is used. These sutures unite the two layers of the peritoneum and make the lower uterine segment extraperitoneal. To avoid the tearing of the suture at the upper angle the uterus is sutured to the peritoneum and fascia, thus fixing it at the upper angle. After the uterus is emptied the wound in the uterine muscle is closed with interrupted sutures of chromic catgut. When infection is present a gauze pack soaked in iodin is placed in the uterus and removed through the cervix and vagina at the end of the operation. After closing the uterus the operator closes the peritoneum with continuous sutures. The results in his eight cases have been satisfactory.

The Care of the Pregnant Woman.—Donald (*Brit. Med. Jour.*, July 8, 1916) believes that the pregnant woman must be taught how to take care of herself and warned of certain dangers that may arise. Those agencies which will give her needed information should be encouraged, such as schools for mothers and other means of education. The practical and theoretical training of midwives should be greatly improved, and a routine examination of the urine must be insisted upon. Improvement in medical education of students, with practical training, is most important, and a residence in a maternity hospital for several weeks is essential. Postgraduate instruction for medical practitioners must be provided, and especially such facilities as will enable them to live in a maternity hospital and receive proper clinical training. Methods of diagnosis, aseptic precautions, and the general treatment of confinement cases must be thoroughly taught. Clinical laboratories in connection with maternity hospitals are essential to study those problems most important in connection with abortion and stillbirth. Maternity hospitals must be provided throughout the country under the charge of obstetricians of experience, who should act as consultants in all difficult cases. Medical officers of health and boards of health and examining boards must coöperate in bringing about these improvements.

Editorial Comment on the Care of the Pregnant Woman.—The *British Medical Journal* for July 8, 1916, considers Donald's paper of sufficient importance to merit editorial comment. Donald's statement that the solution of the matter, namely, the care of the pregnant woman, is not in statistics and notification, but in education and research, is endorsed by the editor. It is acknowledged that medical education in the department of obstetrics should be greatly improved and that clinical facilities and methods of clinical training should take precedence. So far as the care of the pregnant woman and successful production of healthy children is concerned, an important element in the problem lies in the effort to secure bounties given by the state for this purpose. Picard's opinion is quoted that there must be a bonus for every child, and that the birth of another child must not impoverish the family. This in France has amounted to about $20. The editor of the *British Medical Journal* does not pretend to say what the real remedy is in this matter of financial aid for the production of children. He states that it is the greatest problem of the immediate future. There are objections to a great increase in wages, and there are some reasons to hope that an improvement in housing conditions may be of service. The editor does not believe that notification of cases of pregnancy will be of much service, but he cannot escape the opportunity of taking a fling at German Kultur and the German methods of state control.

Syphilis in Relation to Obstetrics.—At a recent meeting of the American Gynecological Soliety, May, 1916, a number of papers upon this subject were contributed. Davis presented a paper reviewing the progress of obstetric science since the discovery of Spirochete pallida and salvarsan. He calls attention to the fact that a practically positive diagnosis can now be made by the discovery of the germ in the tissues of the umbilical cord or the blood from the umbilicus. Latent syphilis is of great importance, as it explains the apparent immunity of the nursing mother toward her syphilitic child. Such a patient, however, is syphilitic, and must be so considered and so treated. While salvarsan is of great value in checking the most acute and virulent stage of syphilis, its use in pregnant women may be followed by abortion, and for a definite and permanent result for mother and fetus, it is inferior to mercury and iodide of potassium. In the present stage of obstetric science we have gained greatly in certainty of diagnosis in the detection of obscure cases, especially those of tertiary syphilis when luetin is of value. We have gained in the treatment of syphilis in its acute stage more than in the other stages. The Wassermann reaction, like the Abderhalden test for pregnancy, is misleading in many conditions, and is not to be relied upon for diagnosis or treatment. When the question of the marriage of syphilitic persons arises, at least six years of thorough treatment and observation are necessary to be reasonably sure of recovery. Repeated negative Wassermann reactions by no means prove that absolute recovery has occurred. Gellhorn and Ehrenfest contributed a paper reviewing a series of cases which they had carefully collected and analyzed from a literature and from their own experience, and the paper is illustrated; in its accurate thoroughness it is a valuable acquisition to obstetric literature. In discussion Williams estimated that 26 per cent. of deaths of children after the first two weeks of the puerperal period were due to syphilis. Among negroes syphilis is four or five times more common than in the whites. Buhman gave the results of his study of various diseases, malignant and otherwise, by the Wassermann reaction. With a few exceptions a strong positive Wassermann reaction very accurately controlled and carefully made is conclusive evidence of syphilis. A weakly positive reaction without clinical evidence of the disease was unreliable. Syphilitic infection might be present with a negative reaction. So far as the observation went, malignant diseases did not give a positive Wassermann reaction. Peterson drew attention to the uncertainties of diagnosis from clinical symptoms alone and histories. Of 290 gynecological patients, 5.6 per cent. gave positive Wassermann reaction. Among these 22 patients but 5 gave a history of syphilis. The frequency of syphilis in women coming to a clinic for obstetrics and gynecology is about 5 per cent. In a mixed hospital it is from 8 to 10 per cent. ADAIR had studied the relation of syphilis to miscarriage and fetal abnormalities. Apparently pregnancy did not end much more frequently during the first three months in those affected with syphilis than in those who were free from the disease. Among premature births there was evidence of syphilis in about one-third of the mothers. Congenital syphilis appeared in 105 of infants born in the hospital. Of 50 premature infants 8 were syphilitic. SLEMONS had found that accurate diagnosis of syphilis in obstetric patients requires the use of both the Wassermann reaction and the study of the placenta. The freshly teased chorionic villi should be examined in every case. If their appearance raised a suspicion of syphilis the placenta must be hardened and studied, and a Wassermann reaction taken with the mother. BAESLACK had studied the question of the relation of the germ to syphilis by experiments upon animals, and believes that this is practically established. C. C. NORRIS reported a case in which he had diagnosed syphilis of the body of the uterus. TAUSSIG had studied syphilitic fever and found that a diagnosis could rarely be made with absolute certainty. Secondary syphilitic fever occurs in a mild form in 20 per cent. of syphilitic patients at the outbreak of the eruption, and sometimes is prolonged and severe. Late secondary syphilitic fever is occasionally seen after confinement or operation. Tertiary syphilitic fever is practically never due to syphilitic lesions in the female genital tract. Apparently this fever is caused by the reaction of the body to the toxins produced by the germ of syphilis. ANSPACH, in 300 patients, gynecological and obstetric, found a positive Wassermann reaction in 22.6 per cent. In cases of stillbirth cases of positive reaction was obtained in 75 per cent. In rectal disease in 50 per cent.; in abortion in 43 per cent.; in pelvic inflammatory cases in 36 per cent.; in fibroid tumors of the uterus in 16 per cent., and in cases of pregnancy in 17 per cent. In the negress syphilis is more common than in the white. FOULKROD described a case of syphilitic fever where salvarsan was given once followed in ten days by the return of fever. A second dose ended the attack.

Cesarean Section for Accidental Separation of the Placenta.—MAYNE (*Am. Jour. Obst.*, 1916, lxxiv), was called to a woman, seven months pregnant, suffering from vaginal hemorrhage. This was but partly controlled by packing, the cervix was small and tightly closed, and the patient was delivered by section. The placenta was almost completely detached and there was a quart of blood and clots in the uterine cavity. The patient made a good recovery.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Iodine Treatment of Pruritus Vulvæ.—The following simple treatment for pruritus vulvæ is warmly recommended by Heusler-Edenhuizen (*München. med. Wchnschr.*, 1916, lxiii, 564) who claims excellent results. In cases with no visible skin changes and with little or no leucorrhea the vulva is thoroughly cleansed as for a vaginal operation, dried, and then painted with a 10 per cent. tincture of iodine. The patient is instructed to exercise the most scrupulous cleanliness; in some cases one treatment suffices, but if necessary it may be repeated. In more advanced cases, with skin changes, such as reddening, swelling, fissure-formation, induration, etc., and more or less severe leukorrhea, every effort should be made to keep the vulvar region dry and free from the vaginal secretion. For this purpose the author uses the dry powder treatment for the vagina, by means of insufflation of zinc oxide or lenicet powder. Externally, the 10 per cent. iodine solution is used followed by dusting with the zinc oxide or lenicet powder. On about the third day the patient returns, when the entire treatment is repeated, then about every fifth day, and at longer intervals as the condition improves, a definite cure usually resulting in about six to eight weeks. The author claims to have healed in this way many cases of long standing, in which the usual ointments, and even *x*-rays, had been tried without avail. The very first application of iodine usually relieves the intolerable itching for a couple of days, but in some cases it produces intense pain, so much so that occasionally an injection of morphine becomes necessary. In most instances this is not required, however, the pain passing off in an hour or so. The author lays great stress on the importance of keeping away all sources of irritation from the vulvar region during the course of the treatment, and especially is the least moisture to be avoided. For this reason the patient is forbidden to bring any water in contact with the genitalia, is directed to avoid sexual intercourse, to keep as quiet as possible so as to minimize perspiration, and after each micturition and defecation to cleanse the parts with cotton soaked in oil, followed by dry cotton to remove all traces of the oil. Three times a day the entire genital region is to be freely powdered by the patient herself. Several case histories are cited to show the effects of the above treatment in refractory cases.

Vaginal Section in Ruptured Ectopic Pregnancy.—In the treatment of the so-called "tragic" cases of ruptured extra-uterine pregnancy, where the necessity for immediate intervention to check hemorrhage is apparent, Babcock (*Am. Jour. Obst.*, 1916, lxxiv, 276) believes that less shock to the patient is caused by a rapid vaginal section and the application of a clamp than by the most dextrously performed laparotomy. His technic is briefly as follows: Under light ether anesthesia with the patient in the lithotomy position the posterior cul-de-sac is opened in the median line by a thrust of a sharp pair of scissors; the index-finger of each hand is then introduced through the opening, which by traction is greatly enlarged. The escaping blood is disregarded; two fingers are immediately introduced into the cul-de-sac and swept to each side of the uterus, locating the tubal enlargement. The diseased tube is freed by sweeping the fingers about it, and when thoroughly isolated it is pulled down through the vaginal incision. A clamp is then applied to the tube and ovary close to the uterus. If the patient's condition permits, ligatures may then be applied, but if not the clamp is simply left in place. The tube and ovary may be cut away distal to the clamp, being careful to leave a sufficiently large pedicle to prevent the friable tissues from slipping out of its grasp. Where the patient is *in extremis*, however, nothing further need be done than the application of the clamp, a piece of gauze being packed sufficiently into the pelvis to isolate the clamp from the intestines and to prevent the edges of the vaginal incision from coming together. A second strip of gauze is placed in the vagina, and the patient returned to bed without irrigation or other maneuvers, the blood in the pelvic cavity being left to drain away gradually. The author says that the entire operation may be performed in from three to ten minutes, and the patient goes off the table with the hemorrhage controlled, and with little increase in the preëxisting shock. The clamp is cautiously opened at the end of forty-eight hours, rotated in each direction, and removed. The gauze is removed on the fourth or fifth day, and the patient sits up at the end of a week or ten days. The author says that in the past ten years he has treated 24 patients by the above method without operative death. One patient died two weeks later from pneumonia, but the final results in all others have been excellent. In no instance was a secondary operation necessary.

Sterilization of Women by Cautery-stricture at the Intra-uterine Tubal Openings.—A rather remarkable method for sterilizing patients where definite indications for this procedure exist and laparotomy is contra-indicated has been proposed by Dickinson (*Surg., Gyn. and Obst.*, 1916, xxiii, 203). It consists, briefly, in causing a stricture at each tubal opening into the uterine cornu by cauterization through the uterine canal. The technic is as follows: The patient is placed in the lithotomy or Sims position, with bladder empty; the cervix is exposed through a Sims speculum and the anterior lip seized and steadied with a tenaculum. About 5 to 10 minims of a 10 per cent. novocaine-adrenalin solution are injected through a Skene pipette into the cervical canal and held under pressure a few seconds. The canal is then wiped with Churchill's tincture or pure carbolic. A sterile uterine sound is then passed into the uterus and turned gently sideways to outline the uterine cavity and find the cornu, an exact note being made of the distance of the latter from the external os. The sound is then withdrawn, and a cautery sound of the same size is bent to the same shape and has its slide pushed up until exactly the same distance is exposed as was measured on the uterine sound. The cautery sound bears on its tip a little spiral or blunt point of platinum which becomes incandescent. The switch is turned on and the platinum heated to show that it is working properly; this is then placed against the cervical mucous membrane in plain sight and a count made of the number of seconds required to burn into the tissues sufficiently to bury the platinum wire. The tip is now allowed to cool, and the sound passed into the uterus to the fundus, being turned to find the cornu as previously determined. The current is then turned on for the number of seconds found necessary to produce the burying effect at the cervix. The other cornu may be done at the same time, or at a second sitting. The author describes this as an office procedure; he lets the patient go home in a short time, advising her to keep quiet the rest of the day and the following day if she has any discomfort. The reaction is slight—possibly a little bloody discharge for a few days, and some discomfort at the next period. There occurs on the cervix a slough and then a clean granulating wound that within two or three weeks is healed over. The author considers that the objections to this method of treatment lie chiefly in unskilled attempts, as insufficient cauterization will not produce complete occlusion. Adhesions of the uterine wall at a lower point than the angle might cause a backing up of menstrual blood, with resulting local hematometra or even hematosalpinx. He thinks that hydrosalpinx of mild degree may arise following correct technic, even when the outer ends of the tubes are patulous, but his is of no serious import. The main difficulty lies in the inability to determine in a given case whether absolute sterilization has occurred; for this purpose Dickinson suggests the injection of a silver preparation into the uterus under pressure and Röntgen examination, to determine if the solution flows out through the tubes, a procedure originally proposed by Cary.

Adenomyoma of the Rectovaginal Septum.—Two cases of this interesting condition are reported by CULLEN (*Jour. Am. Med. Assn.*, 1916, lxvii, 402), these being the fourth and fifth cases that he has observed within a comparatively short time, the others having been reported in papers within the past two years. These peculiar tumors develop in the tissue between the cervix and the rectum, and consist histologically of fatty and fibrous tissue, scattered throughout which are numerous glands resembling exactly those of the endometrium, and often surrounded by small islands of cellular tissue resembling the endometrial stroma. Their importance from a clinical standpoint lies in the fact that from their location, density, and fixation, they are nearly always considered malignant, whereas they are in reality at least morphologically benign, and are practically always amenable to radical removal. In addition to his own cases, Cullen has collected from the literature about a dozen additional ones. They may be roughly grouped into four classes, as follows: (1) Small adenomyomas lying relatively free in the rectovaginal septum; (2) Adenomyomas adhrent to the posterior surface of the cervix and at the same time to the anterior surface of the rectum; (3) Adenomyomas gluing the cervix and rectum together and spreading out into one or both broad ligaments; (4) Adenomyomas involving the posterior surface of the cervix, the rectum and broad ligaments, and forming a dense pelvic mass that cannot be liberated. The ages of the patients ranged from twenty-five to fifty-three years, all the cases occurring in women who were still menstruating. The most pronounced symptom was profuse menstruation, and rectal pain was also a prominent feature in some cases. The treatment advocated by Cullen for these growths depends somewhat upon their condition. Where small discrete nodules exist they may be readily removed through a vaginal incision. Where the growth occupies the posterior surface of the uterus and extends laterally, the ureters should be dissected out carefully and a complete abdominal hysterectomy performed. If the growth is firmly adherent to the rectum, it becomes necessary to remove a wedge of this together with the uterus, and if the lumen of the bowel is greatly narrowed a complete segment of the rectum should be removed, followed by an anastomosis. In desperate cases, such as one that the author experienced, he advises cutting across the sigmoid, inverting and closing the lower end, and making a permanent left inguinal colostomy. At a subsequent operation the uterus, lower portion on the rectum and the broad ligament tissue can then be shelled out as one piece. The author believes that these tumors are by no means as rare as has been commonly supposed, and that closer observation in the future will result in many other instances being recognized.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,
PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

JOHN F. ANDERSON, M.D.,
FORMERLY DIRECTOR OF THE HYGIENIC LABORATORY, PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Pellagra.—The discovery of the presence of small quantities of substances occurring in foods which are essential to the maintenance of health has opened up important problems in diet, with reference to health and disease. These substances are termed vitamins by Funk. They occur in animal as well as vegetable food, in varying amounts. Certain foodstuffs, as polished rice, are extremely poor in vitamins. Others, as meat, are relatively rich in these substances. Beri beri is due to a lack of vitamins, owing to a diet consisting largely of polished rice. Pellagra is presumably also caused by a lack of vitamins.

So far as pellagra is concerned, VOEGTLIN (*Jour. Amer. Med. Assn.*, 1914, lxiii, 1094–1096) concludes that we have to consider: (1) A deficiency or absence of certain vitamins in the diet. (2) The toxic effect of some substances, as aluminum, which occurs in certain vegetable food. (3) A deficiency of the diet in certain amino-acids. The possible relation between aluminum and pellagra was also discussed in a recent monograph by ALESSANDRINI and SCALA (*Contributo unova* *alla etiologia e pathogenesi della Pellagra*, Rome, 1914). These investigators claim that colloidal silica contained in drinking water is one of the most important etiologic factors, in as much as they succeeded in producing lesions resembling pellagra in animals fed on water containing colloidal silica. Colloidal aluminum hydroxid or a mixture of colloidal silica and alumina produced the same results. In view of the fact, as first pointed out by Voegtlin, that aluminum occurs in certain vegetable food in relatively large amounts, the work of the Italian authors furnishes additional evidence that aluminum occupies a prominent position in the etiology of pellagra.

The Significance of Bacillus Coli in Pasteurized Milk.—Shippen (*Jour. Am. Med. Assn.*, 1915, lxiv, 16, 1289) concludes that: As observed by De Graef and De Jong, certain strains of B. coli are not killed by a temperature exceeding that commonly used in pasteurization. The thermal death point of this and similar organisms is not a constant quantity but varies for different strains of the same bacterium. In the case of B. coli communis this variation was found to be as great as 13 degrees. The presence of B. coli in pasteurized milk cannot be taken as an index of its improper pasteurization or subsequent contamination.

The Germicidal Effect of Lactic Acid in Milk.—P. G. Heinemann (*Jour. Infect. Dis.*, 1915, xvi, 3, 479–486). The statement is sometimes found in the literature on sour milk or buttermilk having a germicidal effect on pathogenic bacteria. It has also been intimated that lactic acid producing bacteria are a protection against infectiousness of contaminated milk, inasmuch as the acid produced by these bacteria is said to destroy pathogenic bacteria. There is, however, little positive evidence to show whether this assumption is true or not. Heinemann has studied the question and reaches the following conclusions: Some acid-tolerant cells of Bacillus coli may survive the presence of 0.6 per cent. lactic acid in milk. B. dysenteriæ, B. typhosus, B. diphtheriæ, B. paratyphosus B, and Spirillum choleræ in these experiments were destroyed by the presence of 0.45 per cent. lactic acid. It is possible that strains of these bacteria exist which are able to resist a greater amount of lactic acid. Acid-tolerant strains of B. coli, B. dysenteriæ, B. typhosus, and B. paratyphosus B may multiply in the presence of quantities of lactic acid which are destructive to the majority of cells. The smaller the initial amount of lactic acid, the more likely is the growth of acid-tolerant strains. Consequently, the slower milk sours, the greater is the danger of pathogenic bacteria surviving. The growth of the test bacteria is influenced to a marked degree by the amount of acid present. Up to a fairly definite amount of acid there is an increase in numbers, followed by a decrease, which becomes more pronounced as the amount of acid increases. The amount of acid may increase after the number of bacteria has commenced to decrease owing to the liberation of enzymes. Acid other than lactic acid are frequently present in buttermilk. Buttermilk therefore should be looked upon with suspicion, especially if heavily polluted, unless prepared from pasteurized milk. Still the chances of buttermilk becoming a carrier of infection are much smaller than of raw sweet milk. The presence of saprophytic bacteria in buttermilk may have some influence on pathogenic bacteria. Whether this influence is favorable or otherwise, is difficult to determine by present bacteriological methods.

Studies on Immunization through the Nose.—SEWALL and PEWELL (*Arch. Int. Med.*, 1915, xvi, 605) sensitized guinea-pigs to horse serum by dropping it into the nose. They believe that special advantages accrue through the use of this channel of immunization. When serum was dropped upon the nostril to the amount of 0.1 to 0.2 c.c., and the instillation was repeated at intervals of one to twenty-four days to a total of six doses or less, the animal became affected in one of two opposite directions. When an intravenous injection of about 0.4 c.c. of serum was given sixteen days after the last instillation the pig might die in anaphylactic shock. But in about half the cases the animal survived this large toxic injection. Certain individuals not only survived, but manifested no signs of sensitiveness. It would be clear that the latter animals had not abosrbed the serum through the mucous membrane of the nose were it not that they resist subsequent injections separated by intervals of more than three weeks. The object of the present research was to determine the experimental conditions according to which an animal might be made; on the one hand, anaphylactic or, on the other, refractory to a toxic injection of the antigen. The experiments were applied, especially to determine the effect of the number of separate instillations of serum and the length of the intervals between them on the reactivity of the guinea-pig. No definite relation could be found to exist between these conditions, nevertheless a number of peculiar facts were established. A guinea-pig which has been immunized by nasal instillation and then has received a series of intravenous injections so that the animal tolerates, say, 0.4 c.c. serum with slight reaction, where a long resting period, such as three months, is allowed, the resistance to serum is found to have increased so that two or three times that amount may be equally well tolerated though, as proved by controls, the larger dose would have been fatal at the beginning of the resting period. The serum of pigs thus immunized when injected into normal guinea-pigs did not render them anaphylactic but, on the contrary, showed some power to protect them against toxic injections repeated at intervals of two weeks. The offspring of female immunized animals were markedly or wholly refractory to the intravenous injection of horse serum. A tentative hypothesis is drawn from the experiments, namely, that the biologic response to the introduction of an antigen consists in the development of two opposite-acting antibodies. One, the familiar *allergin* or *anaphylactic* antibody, the other an *anti-allergin* or *protecting* antibody. The present communication must be regarded as simply preliminary to further work.

Cancer-like Growths in Rat's Stomach following Irritation.—Fibiger's announcement of the production of carcinoma in the rat's stomach through the agency of nematodes has not as yet been controverted. F. D. BULLOCK and G. L. ROHDENBURG (*Proc. Soc. Exper. Biol. and Med.*, 1915, xii, 161) record the fact that somewhat similar pictures can be produced by other means of irritation.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
JOHN McCRAE, M.D., M.R.C.P.,
LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL;
SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT,
BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL
VICTORIA HOSPITAL, MONTREAL,

AND

OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH,
PITTSBURGH, PA.

Bacteriological and Experimental Studies on Gastric Ulcer.—Many studies and experiments have been undertaken to determine the pathological process in gastric ulcer. Celler and Thalhimer (*Jour. Exper. Med.*, 1916, xxiii, 791), stimulated by the positive results reported by Rosenow, have repeated the work using his technic in isolating and injecting streptococci into rabbits and cats. The bacteria used in the experiments were isolated from the tissues of eight gastric ulcers and one ulcer at the ostium of a gastrojejunostomy. Histological examination of the human tissues showed the presence of organisms only in or upon the lining of the degenerating tissue of the ulcer. Various microörganisms were observed in this situation. In culture streptococci with other bacteria were isolated in 8, while a staphylococcus and Gram-positive bacillus were obtained in 1. Suspensions of the microörganisms obtained were inoculated into the ear vein or a branch of the gastric artery. In 2 cats a branch of the gastric artery was injected with streptococci. Both animals developed defects of the gastric mucosa which soon began to heal and were completely repaired in thirty-three days. Of the 30 rabbits injected intravenously with streptococci, gastric lesions developed in 4, while 14 showed cardiac lesions. In 8 rabbits a branch of the gastric artery was injected with streptococci and lesions developed in 6. The authors are not convinced that the lesions which they observed in their animals were truly gastric ulcers as there lacked the characteristics of those observed in man. The promptness of healing also strengthened the belief that the lesions in animals and man are not comparable. Embolic lesions in the stomachs of cats healed spontaneously and did not appear to be influenced by the presence of streptococci. They conclude that even though anhemolytic streptococci are present in practically all gastric ulcers it has not been proven that these microörganisms initiate the ulceration or prevent healing.

The Production of Amyloid Disease and Chronic Nephritis in Rabbits by Repeated Intravenous Injections of Living Colon Bacilli.—There is a considerable number of experiments on record in which amyloid has been induced in animals. For its production, bacteria of various kinds as well as chemical substances were made use of. The positive results have been most frequently obtained in rabbits, but successful experiments have also been obtained in dogs, horses, fowl, and mice. Bailey (*Jour. Exper. Med.*, 1916, xxii, 773) found amyloid degeneration in various organs of rabbits during an experimental study of the production of chronic nephritis by B. coli. Living cultures were injected every two to four days into rabbits. In a series of 15 animals positive results were obtained in 8. It was shown that time was an essential element, as no positive case was obtained under eighty-eight days, while every animal treated beyond this time showed amyloid. This product of tissue degeneration was not constant in its reaction to the various tests. It was found that whereas a positive result was obtained with methyl-violet or gentian violet, the iodin-sulphuric acid test was negative or indefinite. This lack in uniformity of the tests has been observed by others studying human material. The presence of amyloid was most commonly observed in the spleen, next the kidney, and finally the liver. As, in this series of experiments, suppuration was not induced in the tissues, it is evident that amyloid, though dependent upon the presence of bacterial growth, need not be associated with pus. The presence of amyloid in the kidney was associated with a subacute and chronic glomerulitis, parenchymatous degeneration, and some interstitial infiltration by round cells. Casts were present in tubules and a moderate fatty degeneration affected the convoluted tubules. The fatty deposit was not observed in association with the amyloid. No definite origin was determined for the amyloid deposit, but the author believed that it was of the nature of an infiltration rather than a production by either fibroblasts or endothelial cells.

Hematogenous Aortitis with Multiple Aneurysms.—Much the greater evidence upon the infection of arteries has been offered by French authors. This is more particularly true of infective arteritis associated with rheumatism. As early as 1840 Bouilland drew attention to the lesions in the heart and arteries as constituting an important phase in this disease. Brault, Stokes, Charcot, Vulpian, Corvisart, and others have described cases in which a more or less intense inflammation of the arterial walls was recognized and in some of which aneurysms had developed. Since 1900 at least 15 different French authors have reported cases and commented upon the presence of aneurysm associated with acute rheumatic fever. The majority of these cases were in young individuals ranging in age from three to twenty years. Soprana and Piazza (*Arch. de méd. exper.*, 1916, xxvii, 55) reported a case with multiple aneurysms of the aorta associated with rheumatism. The patient was a girl, aged twenty-one years, who had never had a previous attack of rheumatism. The fatal attack began suddenly and very acutely. She died within a month after the onset. During her illness she suffered from severe pain and swelling of the joints accompanied by fever. She also had much intrathoracic oppression with dyspnea. She died suddenly. At autopsy three aneurysms were found in the aorta, one of which had quite healthy looking walls and there was no evidence of damage upon the inner surface of the vessel. Microscopically the walls of each aneurysm showed much inflammatory infiltration as well as thickening of the adventitia. The media was much disturbed by the inflammatory processes with the destruction of its essential elements, the muscle and elastic fibers. One aneurysm showed evidence of separation of the adventitia from the media thus forming a type of dissecting aneurysm. In this case the authors were unable to observe any evidence of organic syphilis and the Wassermann reaction was negative. They especially point out the fact that this patient had suffered her first attack of rheumatism during which the aneurysms had developed. They did not determine the nature of the microörganism which had led to tissue destruction. The aortic valves had been the seat of inflammatory reaction, but the infection associated with the aneurysm did not proceed directly along the aortic intima from the diseased valves. The authors believe that the infection of the aortic tissues had occurred by the carriage of the microörganisms to the adventitia. This is the more common mode of infection for these aortic lesions. The aneurysms develop only after the infection and its inflammation have brought about a certain amount of dissolution of the aortic wall.

Progressive Lenticular Degeneration.—New cases of Wilson's disease are periodically appearing in literature. As these cases are reported, the outstanding features of the disease are emphasized. Up to the present no one has analyzed the pathological findings to correlate them with the clinical picture. The constant presence of cirrhosis of the liver with degeneration of the nucleus lentiformis has not received adequate explanation. FARNELL and HARRINGTON (*Jour. Lab. and Clin. Med.*, 1916, 1, 561) have added another case to this interesting group. The patient was a girl of nineteen years who for four years had epileptoid seizures in which incoördination of the muscles of the extremities was one of the marked features. Her gait was somewhat spastic and at times her posture was fixed. Her mental development was below normal. At autopsy the striking finding was a marked cirrhosis of the liver of the portal type and the loss of the characteristic markings of the corpus striatum on the left side. The left caudate nucleus was smaller than normal and there was some dilatation of the left ventricle. The degeneration in the region of the nucleus lentiformis gave an appearance as if the various structures of this part were confluent. Small areas of necrosis were also present in this region. The microscopic examination of the affected brain tissues showed an increase of the glial tissue. The evidence of this degeneration was much more marked on the left than on the right side. There was no disturbance of the motor cortex or the cells of the anterior horns. The vessels were not sclerosed. The entire reaction appeared to be one of replacement gliosis which had not gone on to complete disintegration with cavity formation.

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ORIGINAL ARTICLES

THE SUSCEPTIBILITY OF MAN TO FOREIGN PROTEINS.[1]

By Warfield T. Longcope, M.D.,
NEW YORK.

(From the Medical Clinic, Presbyterian Hospital, Columbia University, New York.)

Throughout the literature of the last century one may find isolated statements regarding the unexpected effects upon certain individuals of substances now recognized as containing proteins, and perhaps the most significant of these are the observations of Blackley, in 1873, on the effect of grass pollens upon the nasal mucous membrane, conjunctivæ, and the scarified skin of individuals suffering from hay fever. About 1869 and 1870, when transfusions of sheep's blood were much in vogue, it was frequently noted that an urticaria appeared as a late effect of this treatment. It was not, however, until the introduction of diphtheria antitoxin in 1894 that the results of injections of foreign proteins in man received serious study. Lublinski,[2] in the year 1894, described what is now the perfectly familiar picture of serum disease as a sequel to the injection of diphtheria antitoxin, but not until the careful investigations of von Pirquet and Schick,[3] in 1905, was any important light thrown upon the process. They immediately recognized the importance which the so-called antibodies against foreign protein, in this instance horse serum, might have in the production of serum disease, and the subsequent observations and experiments by Otto, Rosenau and Anderson, Gay and Southard, Friedemann, Doerr, Friedberger and a host of others[4] have made it quite clear that the introduction of native foreign protein follows essentially the same biological and chemical physical principles in man as in the lower animals.

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[1] Lecture delivered before the Harvey Society, New York, February 26, 1916.

[2] Deutsch. med. Wchnschr., 1894, xx, 854.

[3] Die Serumkrankheit, 1905.

It is only necessary to point out here that the introduction of the long series of foreign proteins that have been subjected to experiment is followed by the production in the animal body of various antibodies which have the power to unite with the original substance or antigen to produce a new effect. This new effect may be obvious and best studied by mixing antibody and antigen outside the body, as is the case with the hemolysins, the bacterial agglutinins, bacteriolysins, and precipitins; it may be obtained both *in vitro* and *in vivo*, as is the case with antitoxin, or it may be demonstrable almost exclusively in the animal body, as is the case with anaphylaxis.

The bare outlines of the experiments from which our knowledge of anaphylaxis has been derived may be summed up in a statement of the following condition: An animal is injected subcutaneously, intraperitoneally, or intravenously with a small amount of foreign protein, for example horse serum. This produces no visible effect. If, however, after an interval of at least nine to fourteen days, a second injection of the same protein is made the animal becomes ill immediately, presenting characteristic symptoms which differ only slightly for different species; while if the dose of serum is properly gauged and made into the peritoneum or vein the animal dies within five minutes to one hour. This is known as active anaphylaxis. Second, the condition known as passive anaphylaxis, first described by Gay and Southard,[5] Otto[6] and Friedemann,[7] who showed that the blood of an animal sensitized to horse serum confers this specific sensitiveness to a normal guinea-pig. Sensitiveness develops in the normal animal after a period of fifteen to eighteen hours following the inoculation of the serum from the sensitized guinea-pig, and lasts a few days or at most weeks. It is dependent upon the presence in the blood of the actively sensitized animal of antibodies for the specific proteins which are thus transferred passively to the normal guinea-pig. This transfer may take place during pregnancy from mother to offspring. Third, the state termed anti-anaphylaxis by Besredka and Steinhardt,[8] in which for a short period following the anaphylactic shock the actively sensitized animal becomes insensitive to injections of horse serum. Following this period of anti-anaphylaxis an animal may again become sensitive to the specific protein and remain so for months or years. Finally, it was shown by Rosenau and Anderson[9] that the repeated injection of horse serum at intervals of two or three days produced a refractory condition toward subsequent injections of the specific protein, so that for a long period of time they no longer react to such an injection with anaphylactic symptoms. This refractory state, however, finally gives way to sensitiveness, and eventually the animal is again susceptible. During the refractory state, which has been called one of immunity, antibodies for horse serum may be present in great concentration in the serum, and when injected into normal guinea-pigs will passively sensitize them to the protein.

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[4] For full bibliography see: Doerr, Wassermann and Kolle, Handb. d. path. Microorg., 1913, ii, 947. Richet, L'Anaphylaxie, 1912. von Pirquet, Arch. Int. Med., 1911, vii, 259, 383. Friedemann, Jahresb. u. Immunitätsf., 1910, vi, Abst. i, 31. Besredka, Ibid., 1912, viii, 90. Vaughan, Protein Split Products in Relation to Immunity and Disease, 1913. Rosenau and Anderson, Arch. Int. Med., 1909, ii, 579. Otto, Wassermann and Kolle, Handb. d. path. Microorg., 1908, ii, 255. Auer, Forchheimer's Therapeusis, 1914, v, 39.

[5] Journal of Med. Research, 1907, xi, 143.

[6] München. med. Wchnschr., 1907, liv, 1665.

[7] Ibid., 2414.

[8] Ann. de l'Inst. Pasteur, 1907, xxi, 117, 384.

After this brief statement of the fundamental principles of anaphylaxis it is possible to consider in more detail the process as it develops in man, for the introduction of antitoxic and antibacterial sera has given ample opportunity for an exact analysis of the effect of single and repeated injections of foreign protein. This, as a rule, has been horse serum, though the serum from any foreign species will give the same results. As in an animal, so in man, primary injections of horse serum given by any route produce no immediate symptoms. In the vast majority of instances it remains, as can be shown by the presence of precipitinogen and by anaphylactic methods in the circulation, for long periods of time, and is excreted very slowly, if at all, by the kidneys. For a period of six to ten days following primary injection, known as the incubation period, there is nothing to be observed, but at any moment after the sixth day typical serum sickness may appear. (See Chart.)

The symptoms and signs of this disease are as striking and characteristic as any natural disease process with which we are familiar. Usually a skin eruption with intense itching preceded by glandular enlargement ushers in the attack. The eruption starts, as a rule, at the point of inoculation, but spreads rapidly over the entire body. Urticaria is most common, but there may be a patchy or diffuse erythema, scarlatiniform rashes, or a multiform eruption. Edema of the face and ankles is usual and may affect the entire body. In rare instances it is localized to the pharynx or larynx, and in one instance a transient hemiplegia was supposed to be caused by local edema of the meninges. The temperature is elevated, and there is general malaise and headache with prostration, though rarely nausea or vomiting. Joint pains are very common in severe cases. They are always multiple, and though the pain is exquisite on motion, there is little tenderness and no swelling or reddening.

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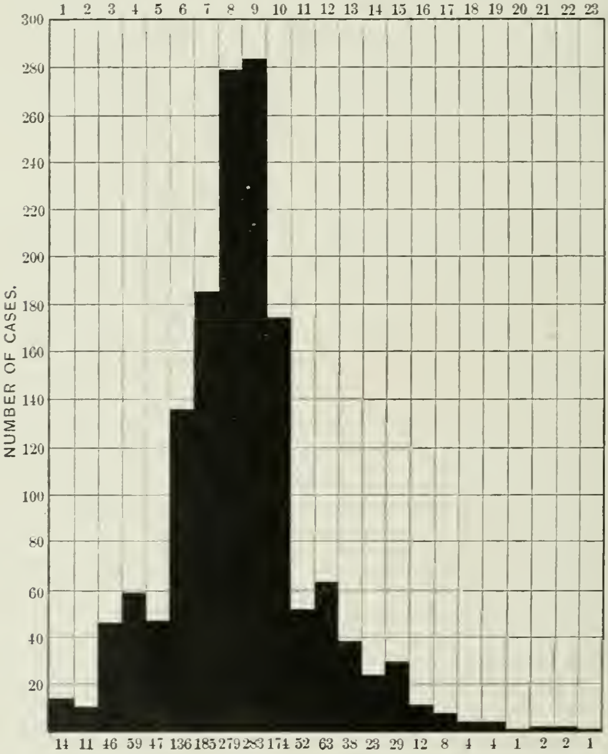
[9] Bull. 29, Hyg. Lab. U. S. P. H. and M. H. S., 1906; Bull. 36, Hyg. Lab. U. S. P. H. and M. H. S., 1907.

Quite regularly the lymph nodes are enlarged, they are often swollen to the size of walnuts in the region draining the primary injection, and may be excessively tender. The spleen is sometimes enlarged; in 5 to 9 per cent. of the cases there is albuminuria, and, as I shall point out later, there are often disturbances in the functional activity of the kidneys. Examination of the blood, according to von Pirquet, shows a primary polymorphonuclear leukocytosis with subsequent leukopenia and absolute increase in the lymphocytes. The disease may last for twenty-four hours to twenty days or longer. In the severest cases there are one to four relapses which usually occur after the use of large amounts of serum, and come, according to Axenow,[10] at ten day intervals.



Incubation period in 1493 cases of Serum Disease. Figures at top indicate number of days after injection of serum. Bottom line of figures represents number of cases.

The occurrence, intensity, and duration of the disease depend, upon several factors: First, upon the amount of serum used. The disease is not usual after small doses, but is extremely common after large ones. The statistics of Weaver,[11] based on a study of 801 reported cases, show an incidence of 10 per cent. after the injection of 1 to 10 c.c. of serum. Most of the attacks are mild, but the incidence increases in almost direct proportion to the amount of serum used, until, when quantities over 90 c.c. are employed, 75 to 100 per cent. of the patients develop serum disease. Secondly, it seems possible, from the statistics of Bokay[12] and Schulz,[13] that the incidence may depend to some extent upon the source of the serum. Apparently certain horses yield a serum which is much more likely to be attended by serum disease than others. And finally the individual characteristics of the patient play a role, for the same dose of serum from the same source may produce quite different affects in different persons.

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[10] Jahrb. f. Kinderh., 1913, lxxviii, 565.

A second injection of serum before the tenth day or before the onset of serum disease is not attended by immediate symptoms. It has already been observed that in the case of animals, repeated injections of horse serum at two- to three-day intervals produce a condition which makes them refractory to subsequent injections, which state may last many weeks. By the same method in human beings the incubation period for serum sickness may be prolonged for weeks, but its final appearance cannot always be prevented, and after these multiple doses at short intervals the attack, when it appears, is, according to Goodall,[14] especially severe. If, however, a second injection is made after the tenth day, von Pirquet and Schick have shown that the following reactions may occur: (1) The local immediate reaction. Within fifteen minutes to an hour after subcutaneous injection of serum, edema, erythema, or urticaria appears at the site of inoculation. (2) The general immediate reaction which is characterized by a more or less severe general reaction coming on within twelve to twenty-four hours after the inoculation and having the characteristics of a fulminant case of serum sickness. The most violent and general immediate reactions are accompanied by such symptoms as dyspnea of asthmatic type, cyanosis, collapse, nausea and vomiting, and suppression of urine, symptoms which are not regularly seen in the ordinary form of the disease. (3) The accelerated reaction or form in which the incubation of the serum sickness falls between the immediate reaction and the ordinary reaction and comes on within a period of three to five days after inoculation, and finally the second injection may be followed simply by the normal form of serum sickness. Any of these reactions may occur separately or may be combined in one and the same patient.

The actual occurrence of the immediate general reaction following a second injection varies according to different observers. It is noted most often, according to von Pirquet and Goodall, between the thirty-fifth and eightieth day after the primary inoculation of serum, and occurs when serum is injected in large quantities at this period in about 60 per cent. of the cases. An injection made after three months is usually followed by an accelerated reaction, and when years have elapsed the general reaction may be of the ordinary type. The immediate reaction, though it may be severe, has, as far as I know and as the statistics of Park[15] and Nemmser[16] and Cuno[17] show, never caused death when the inoculation is made subcutaneously. Following a second intravenous injection, however, Koch[18] has reported one death. After the second injection of serum made in the spinal canal, coma, convulsions, and death have been reported by Hutinel,[19] Grysez and Dupuich,[20] and Archard and Flandin.[21] Auer[22] has recently analyzed all these cases and considers that death is not due to true anaphylactic shock. The symptoms are certainly not those of a general immediate reaction, but it seems possible that a local immediate reaction may occur, similar to that in the skin which might produce extensive edema of the meninges, and in this way account for the symptoms as they are described.

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[11] Arch. Int. Med., 1909, iii, 485.

[12] Deutsch. med. Wchnschr., 1911, xxxvii, 9.

[13] Berl. klin. Wchnschr., 1914, li, 349, 401.

[14] Jour. Hyg., 1907, vii, 607; British Med. Jour., 1913, ii, 1359.

The local immediate reaction upon second injection is specific, as was shown by von Pirquet, and is analogous to the Arthus phenomenon in the rabbit. Lucas and Gay[23] describe it as a very frequent occurrence in children receiving prophylactic doses of diphtheria antitoxin at three weeks' intervals. Moss,[24] in 1910, drew attention to the value of this immediate cutaneous reaction in determining the presence of sensitiveness to horse serum in persons who had previously been injected and found that five of twenty-one such patients reacted positively to an intracutaneous injection of horse serum two to three years after the primary injection. The exact time of appearance of this immediate reaction for skin sensitiveness has been studied by Hamburger and Pollok,[25] Michaels,[26] and Cowie.[27] By making intradermic injections of 0.1 to 0.5 c.c. of serum at short intervals these observers have noted its appearance on the fifth day after the injection of serum and its persistence for years after. Michaels makes the important observation that the reaction cannot be obtained during serum sickness, and in two instances when it was possible to obtain a positive skin reaction before the onset of the disease it disappeared during the course of the serum sickness. Immediately after the serum sickness all observers agree that the skin reaction rapidly increases in intensity, and when the test is properly performed it is obtained in 80 to 90 per cent. of the cases even for years after.

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[15] Tr. Assn. Amer. Phys., 1913, xxviii, 95.
[16] Deutsch. med. Wchnschr., 1913, xxxix, 740.
[17] Ibid., 1914, xl, 1017.
[18] Berl. klin. Wchnschr., 1915, lii, 685.
[19] Presse méd., 1910, xviii, 497.
[20] Bull. et mém. Soc. méd. d. hôp. de Paris, 1912, xxxiii, 371.
[21] Compt. rend. Soc. biol., 1912, lxxiii, 419.
[22] Forchheimmer's Therapeusis, 1914, v, 39.
[23] Jour. Med. Research, 1909, xx, 251.
[24] Jour. Am. Med. Assn., 1910, lv, 776.
[25] Wien. klin. Wchnschr., 1910, xxiii, 1161.
[26] Arch. Mal. d. Enfants, 1913, xvi, 835.
[27] Am. Jour. Dis. Child., 1914, vii, 253.

Dr. Rackamann and I have employed this method to determine the development of skin sensitization in serum disease. The test dose has been very small and injected intradermally, 0.02 c.c. of pure serum and of serum in $\frac{1}{10}$ and $\frac{1}{100}$ dilutions has been employed. After these minute doses skin sensitiveness does not appear until serum disease has set in, but once having made its appearance the reaction increases in intensity and has been present by the fifteenth to twentieth day in most instances. A reaction of equal intensity has been obtained in several adults two or three years after an injection of antitoxin. The intradermal method is much the most sensitive of any of the cutaneous tests, and may be strikingly positive with serum in $\frac{1}{100}$ or $\frac{1}{500}$ dilution, although the scarification method such as used for tuberculin by von Pirquet gives a negative response with undiluted serum. It is, as far as we have observed, specific and cannot be brought about in these cases by the use of various other animal sera, egg-white, casein, or vegetable proteins. It consists in the appearance after a period of ten to fifteen minutes of an elevated, yellowish, firm wheal, surrounded by a bright red erythematous areola. This increases rapidly in size until the wheal reaches at the end of thirty to forty-five minutes 1 to 2 cm. in diameter, and the erythematous zone 3 to 6 cm. in diameter. During this period the patient often complains of itching at the site of inoculation. At the end of an hour the reaction fades and in twelve hours nothing is to be seen. Salt solution, human sera, and various other animal sera result in the formation of a minute white papule 5 to 6 mm. in diameter, about which there may appear a narrow red zone. This traumatic reaction fades in five to fifteen minutes, and is almost invisible at the end of half an hour when the true reaction is at its height. Knox, Moss, and Brown[28] have found that under similar conditions a skin reaction is obtained in the rabbit. It makes its appearance first on the eleventh day after primary inoculation of serum, and is present in most cases by the sixteenth to twenty-second day. It differs from the reaction in the human being in that the development is much slower, attaining its height only after twelve to twenty-four hours, while it persists much longer, lasting two or three days. The skin reaction must be considered as a delicate and probably specific reaction of an individual artificially sensitized to a foreign protein, and makes its appearance from five to fifteen days after the primary injection.

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[28] Jour. Exp. Med., 1910, xii, 562.

At about the time that this sensitiveness appears, and sometimes immediately before the onset of the serum disease, other reactions occur which are considered evidence of the formation of antibodies to the foreign protein. These are represented by the appearance in the blood serum of precipitins for the foreign protein and the substance which is capable of transmitting the sensitive state passively from one animal to the other. Hamburger and Moro,[29] who first demonstrated precipitins for horse serum in the blood of cases of serum disease, and Doerr and Russ,[30] as well as Weil,[31] experimenting later in animals, have attached much importance to the precipitins as a part of the anaphylactic reaction, though von Pirquet was inclined to regard the production of precipitins as an accompanying phenomenon rather than as one upon which anaphylaxis is dependent. C. Wells,[32] has followed the curve of production of these antibodies during serum sickness in children receiving diphtheria antitoxin. In some cases precipitins are demonstrable about the sixth day after injection of serum and before the sickness starts, but with the onset of serum sickness the precipitins diminish or disappear to increase rapidly after the disease to a high degree of concentration. A diminution again takes place sixteen days later, and finally the precipitins can no longer be demonstrated.

More closely related to the anaphylactic state than the precipitin is the presence of the substance which is capable of causing passive sensitization, variously designated immune substance, anaphylactic antibody, anaphylactin, or allergin. Though Doerr and Russ[33] have undertaken to measure quantitatively the amount of this antibody in a given specimen of serum, there are certain factors, as has recently been shown by Lewis,[34] which complicate such a quantitative analysis of the anaphylactic antibody, and consequently the result obtained from passive transfer can only roughly measure the actual amount of this substance in the actively sensitized animals. That there is some parallelism between the amount of precipitin and quantity of anaphylactin has been shown by Burkhardt,[35] but when several injections of serum are given to sensitize actively the two reactions do not run parallel. Weill, Hallé, and Lémaire[36] found that the blood of rabbits receiving a single injection of horse serum showed the power to transmit the anaphylactic antibodies to guinea-pigs after the lapse of ten days. This increased in intensity up to the twenty-fifth day, and gradually disappeared after the sixtieth day. When, however, repeated injections of horse serum were employed at two months' intervals the ability of the rabbits' serum to sensitize guinea-pigs appears immediately after the last injection, but does not persist as long. Anderson and Frost[37] found that the blood of guinea-pigs contained "anaphylactin" for as many as four hundred and fifty days after sensitization, and as Rosenau and Anderson originally noted, guinea-pigs made refractory to anaphylactic shock by repeated injections of horse serum, still carry in their serum anaphylactic antibodies in large amounts. Attempts to demonstrate this phenomenon in man have met often with indifferent success. Anderson and Frost,[38] as well as Archard, Flandin,[39] Weil,[40] and Yamanouche[41] report isolated successful results, but Novotny and Schick[42] obtained positive results in only 2 out of 12 cases. Gryez and Bernhard,[43] however, were more successful, and with the blood drawn from eleven children five to two hundred and thirty-four days after injection of diphtheria antitoxin were able to sensitize guinea-pigs passively to horse serum. Dr. Rackamann and I have made some observations upon the appearance of this anaphylactic antibody in ten individuals receiving horse serum. We have found that the anaphylactin was present in one or two instances before the appearance of serum disease, but in the vast majority of cases it is only demonstrable at the subsidence of the symptoms. Once having appeared at this time, however, it may persist for many days and be present in such concentration that one can readily transfer the sensitiveness from man to a guinea-pig.

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[29] Wien. klin. Wchnschr., 1903, xvi, 445.

[30] Ztschr. f. Immunitätsf., orig., 1909, iii, 181. Doerr, Wassermann and Kolle, Handb. d. path. Microörg., 1913, ii, 947.

[31] Jour. Immunol., 1916, i, 1, 19, 35, 47.

[32] Jour. Inf. Dis., 1915, xvi, 63.

[33] Loc. cit.

[34] Jour. Inf. Dis., 1915, xvii, 241.

[35] Ztschr. f. Immunitätsf., orig., 1910, viii, 87.

[36] Compt. rend. Soc. de biol., 1908, lxv, 141.

It will thus be seen that toward the end of the incubation period of serum disease, certain antibodies and immune reactions, namely, the skin reaction, the precipitin reaction and anaphylactin, can occasionally be demonstrated in the blood serum. With the appearance of the symptoms they diminish or disappear to reappear with great intensity at the subsidence of the attack. Since the serum or antigen during this entire period may still be demonstrated in the circulation, it is highly probable, as was proposed by von Pirquet, that serum disease is brought about by a union of the rapidly forming antibodies and the circulating antigen. The theoretical explanation as to the place and cause of this union has been the subject of much discussion. The union, of course, may take place in the circulating blood, thus liberating toxic substances that produce the symptoms of serum disease or anaphylaxis; second, the union may occur in the tissues and cells of the body; or, third, it may proceed in both situations. Friedberger, who has experimented extensively along this line, has advanced first one and then the other view, and in the human being the appearance of precipitins and the anaphylactic antibodies in the blood stream before the onset of serum disease, might lead one at first to suppose that the reaction was principally in the circulating blood, as was the original idea of von Pirquet. The observations of Pearce and Eisenbrey,[44] of Schulz[45] and those of Dale,[46] which have been extensively amplified and confirmed by Weil,[47] show definitely that the cells of sensitized animals, and certainly the smooth muscle of the uterus, freed from all traces of the body fluids, are capable of reacting violently when brought in contact with the specific antigen toward which the animal is sensitive. The original observation of Rosenau and Anderson repeatedly confirmed that the blood serum of an animal made highly refractory by repeated injections of horse serum may still contain large amounts of anaphylactic antibody, is in support of the idea at present quite widely accepted that the presence of these antibodies in the serum is a source of protection rather than harm. Circulating in the blood in large quantities they unite slowly with the reinjected antigen or at least "fix" it so that the antigen as such is prevented from coming in contact with the cells of the body. The facts which have been brought out in the study of serum disease in man might be interpreted in the light of either theory.

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[37] Bull. 64, Hyg. Lab. U. S. P. H. and M. H. S., 1910.

[38] Loc. cit.

[39] Loc. cit.

[40] Proc. Soc. Exp. Biol. and Med., 1914, xii, 37.

[41] Compt. rend. Soc. de biol., 1910, lxviii, 1000.

[42] Ztschr. f. Immunitätsf., orig., 1909, iii, 671.

[43] Comp. rend. Soc. de biol., 1912, lxxiii, 387.

The onset of serum disease is probably, therefore, a visible evidence of the development of general sensitiveness and represents a more or less violent reaction between the circulating antigen and antibody which is in process of development, certainly in the cells, but possibly too in the circulating blood. It is followed by a rapid expulsion of antibodies into the circulation, and shortly afterward by a period of hypersensitiveness, at which time the reinjection of serum may call forth a violent general reaction. Subsequently this period of hypersensitiveness diminishes and antibodies may disappear from the circulation. The injection of serum at this time, owing to the slight concentration of antibodies, does not produce an immediate general effect, but excessive antibody formation under these circumstances, as von Pirquet and von Dungern have shown in the case of precipitins, is much more rapid than in the normal individual and the general reaction, or accelerated serum sickness, appears. Finally, with a complete loss of sensitiveness, the individual returns to the normal state and the reaction is of the normal type.

There is not time to discuss the question as to whether the union of antibody and antigen is of chemical nature, whether it depends upon fermentation, or whether, as is the view that Zinsser[48] has brought forward, some change in the physical properties of the serum determines the union of these two substances. To elucidate the actual nature of the toxic substance that is formed by this union, much thought and experimentation have been expended. It is only a step from the early observations of Pfeiffer,[49] and Wolff-Eisner[50] upon the poisonous products of bacterial disintegration to the work of de Waele,[51] Biedl and Kraus,[52] Vaughan,[53] Friedberger,[54] Weichardt and Schittenhelm,[55] and many others who have shown that the products and by-products of protein digestion when injected into various animals may cause symptoms almost identical with true anaphylactic shock. These observations soon suggested that with the union of antibody and antigen the antigen or foreign protein is digested to form poisonous split products. To confirm this idea evidence has been brought forward by Abderhalden,[56] Cammerer and Pincussohn,[57] by Pfeiffer and Jarish,[58] G. Zung and György[59] and by Jobling and Petersen,[60] to show that during anaphylactic shock in dogs products of protein digestion appear and that the non-protein nitrogen, together with the proteose of the serum, are distinctly increased.

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[44] Tr. Cong. Am. Phys. and Surg., 1910, viii, 402.

[45] Jour. Pharmacol. and Exp. Therap., 1910, i, 549. Bull. 80, Hyg. Lab. U. S. P. H. and M. H. S., 1912.

[46] Jour. Pharmacol. and Exp. Therap., 1913, iv, 167.

[47] Jour. Med. Research, 1914, xxx, 87, 299.

[48] Arch. Int. Med., 1915, xvi, 223.

So far we have discussed only artificial sensitization in man, but it is now necessary to direct attention to a state in which sensitiveness to foreign proteins exists without the known introduction of these proteins. It has been repeatedly observed that the first injection of any foreign serum may be attended in man by a violent immediate reaction. One of the earliest instances to come into prominent notice was the immediate death of Prof. Langerhans's young son after receiving for the first time an injection of diphtheria antitoxin. Gottstein[61] reported a few such cases in 1896, and in 1909 Gillette[62] collected from the literature 30 in which sudden collapse or death followed immediately upon the first injection of antitoxin. It is important to note that 22 of these cases gave a history of asthma or of some respiratory disease. The patient immediately after the injection shows great uneasiness; perhaps complains of constriction in the chest; has violent dyspnea; the face swells and becomes purple; he falls in collapse and may be dead in five to ten minutes. In attacks which are somewhat less fulminant there is violent asthma, cyanosis, collapse, and a giant urticarial eruption. These perhaps are the most striking and certainly terrific demonstrations of spontaneous sensitiveness to foreign protein, but they only represent one of the many such sensitizations which have been long recognized as idiosyncrasies. The early work in 1873 of Blackley[63] upon hay fever I have already mentioned. It is of considerable historical interest to note that he associated this condition as early as 1853 with the inhalation of pollen grains, and showed definitely that the instillation of certain pollens in the nose and eye produced in hay fever patients edema and congestion of the mucous membrane with lacrimation. He also made the important observation that pollen grains rubbed into a scarification of the skin called forth an intense itching and local edema. The work of Dunbar,[64] in 1903 and 1904, showed that this was a specific reaction, and later Weichardt[65] brought out the fact that it was due to the protein of the pollen. From this it was only a step for Wolff-Eisner,[66] in 1906, to suggest that hay fever had its origin in sensitization to proteins of various pollens, and later to apply this principle to the explanation of the origin of the urticarias succeeding the ingestion of certain foods.[67]

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[49] Ztschr. f. Hyg. u. Infektionkrankh., 1892, xi, 293.

[50] Centralbl. f. Bakt., 1904, xxxvii, 390, 566, 684.

[51] Bull. Acad. Roy. de Méd. de Belgioue, Brux., 1909.

[52] Wien. klin. Wchnschr., 1909, xxii, 363.

[53] Loc. cit.

[54] Ztschr. f. Immunitätsf., orig., 1911, ix, 369.

[55] Ztschr. f. exp. Path. u. Therap., 1912, x, 412, 448; xi, 69.

[56] Ztschr. f. physiol. Chem., 1912, lxxxii, 109.

[57] Ibid., 1909, lix, 293.

[58] Ztschr. f. Immunitätsf., orig., 1912–13, xvi, 38.

[59] Ibid., 1915, xxiii, 402.

[60] Jour. Exp. Med., 1915, xxii, 401.

[61] Therap. Monatsh., 1896, x, 269.

[62] New York State Med. Jour., 1909, ix, 373.

So common, indeed, is this conception of protein sensitization that attempts have been made to explain thereby all physiological and pathological processes from childbirth to epilepsy. But in spite of these unwarrantable views it is certainly an important factor in some pathological processes, and for this reason it is highly essential that we should understand accurately what true protein sensitization means and analyze the hypotheses that may be evolved from this fascinating but very obscure subject.

A survey of the literature brings forth many interesting examples of what seem to be true spontaneous susceptibility to various foreign proteins. The symptoms produced from contact with these proteins are usually referred to the respiratory tract, the gastro-intestinal tract, and the skin. Hay fever is the example of protein sensitization most thoroughly studied in which the symptoms brought on by contact with foreign proteins are usually confined to the respiratory tract and the conjunctivæ. In a certain proportion of cases of asthma the attack simulates, as the fundamental experiments of Auer and Lewis[68] suggested to Meltzer,[69] mild anaphylactic shock in the guinea-pig, and as has been demonstrated since, it may be precipitated by inhalation, subcutaneous injection, or ingestion of foreign proteins to which the individual is sensitized. The most striking examples are to be found in the patients whose attacks invariably occur when they come in close contact or even in the near vicinity of such animals as horses, dogs, cats, rabbits, or mice; or in patients who develop from their hay fever true paroxysms of asthma. The subcutaneous injection of even the minutest quantities of solutions of these proteins will precipitate violent paroxysms of asthma, and it is in such spontaneously sensitized individuals that the first injection of diphtheria antitoxin has produced violent symptoms or death.

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[63] Experimental Researches on the Cause and Nature of Hay Fever, London, 1873.

[64] Deutsch. med. Wchnschr., 1903, xxix, 149.

[65] Centralbl. f. Bakt., 1906, xxxviii, 493.

[66] Dermat. Centralbl., 1907, x, 164.

[67] Wolff-Eisner, Das Heufiener. München, 1906.

[68] Jour. Exp. Med., 1910, xii, 15.

[69] Tr. Assn. Am. Phys., 1910, xxv, 66.

The gastro-intestinal disturbances dependent upon sensitization to eggs, which is not uncommon in children, and may occur in adults, has been studied, especially by Schloss,[70] Lesné and Richet fils[71] and Talbot.[72] Sensitization to cow's milk, as recently pointed out by Kleinschmidt[73] is another cause of gastro-intestinal disturbances in children. H. L. Smith[74] first drew attention to the importance of sensitization in a case of buckwheat poisoning and similar symptoms after eating such foods as strawberries, melons, or other fruits or vegetables, certain form of meats and shellfish, are widely recognized and are familiar as idiosyncrasies.

Various skin eruptions are associated with direct or indirect contact with foreign protein. In some instances an urticarial eruption always follows contact with the fur of one or another animal or the juice of plants. Wechselmann[75] has described a form of dermatitis which comes on in satinwood workers ten to fourteen days after they start their work. Talbot and Lesne and Richet have especially called attention to eczema which so frequently is seen in children sensitive to egg-white and milk. An increased susceptibility which Goldschmidt[76] has described, to the irritating odor and juices coming from the living ascaris, is probably to be classed with these cases.

A few instances of hypersensitiveness to the sting of insects are described. I know of one individual in whom the sting of the mosquito produces enormous areas of edema similar to the so-called angioneurotic form, and in another case a sting of a wasp was followed by symptoms exactly like the immediate reaction in serum disease. Great local swelling with erythema and edema, collapse, general urticaria; joint pains appeared immediately on two occasions after this individual was stung. Finally, there is a very definite group of cases, of which I have seen several, in whom suddenly, without assignable cause, the patient is stricken with an illness which is precisely like serum disease, and which may recur at the end of several months. At the onset there may or may not be nausea and vomiting, but always there is a general urticaria associated with slight fever, swollen tender lymph nodes, arthralgia, and usually a mild albuminuria. Indeed, some of the attacks of Hennock's purpura are not unlike serum disease, and we have found at least one case sensitive to several foreign proteins. Even more obscure pathological processes, such as eclampsia, have been explained upon the basis of protein sensitization, in this instance, to the chorion or fetal tissues; but the evidence for such assumptions at the present time does not admit of further discussion of these very obscure conditions.

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[70] Am. Jour. Dis. Child., 1912, iii, 341.
[71] Arch. d. mal. d. infants, 1913, xvi, 81.
[72] Boston Med. and Surg. Jour., 1914, clxxi, 708.
[73] Monatsh. f. Kinderh., 1913, xi, 644, orig.
[74] Arch. Int. Med., 1909, iii, 350.
[75] Deutsch. med. Wchnschr., 1909, xxxv, 1389.
[75] München. med. Wchnschr., 1910, lvii, 1991.

Reference must be made here to the interesting drug susceptibilities which apparently may be spontaneous or acquired after the repeated subcutaneous or intravenous use of certain chemicals. In this connection reactions to the iodin and arsenic compounds have been most carefully studied. Stäubli[77] and Kaufman[78] have called attention to the increasing local inflammation which patients are likely to experience after repeated injection of cacodylate salts. With the introduction of salvarsan many observers have noticed anaphylactic-like symptoms during the intravenous administration of this drug. Iwaschenzoff[79] has reported many such instances, and Draper,[80] who has observed it in about 55 per cent. of all treated cases, states that it is never noted at the first injection, rarely at the second, and that if it occurs at all it usually does so at or after the fourth. The patient complains of oppression in the chest, is restless, has dyspnea, shows suffused face and conjunctivæ, and cyanosis. Afterward there may be vomiting and occasionally a blotchy urticaria appears.

Up to the present time it is not known that antibodies are produced by any substances other than those which contain a high protein molecule, and at first the explanation of these reactions was difficult. Friedberger and Ito[81] have called attention to the fact, however, that the serum of a guinea-pig may be so altered by treatment with the tincture of iodin that a mixture of the two will sensitize the guinea-pig to subsequent injections of the same mixture of its own serum and iodin or sodium iodin or to Logul's solution. A first injection of Lugol's solution sensitizes to this mixture of serum and iodin but not to potassium iodin or to Lugol's solution alone. Swift[82] has been able to obtain essentially the same results with salvarsan, and the explanation given by these observers for the iodiosyncrasies to iodides and the anaphylactic-like symptoms after the intravenous injection of salvarsan is that the combination of the drug with the patient's serum forms a new protein compound to which he may be actively sensitive. The reports by Bruck[83] and Klaussner[84] of passive sensitization with the serum of patients showing drug idiosyncrasies have been disproved by Zieler[85] and Pöhlmann.[86]

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[77] Deutsch. med. Wchnschr., 1912, xxxviii, 2452. [78] Ibid., 1913, xxxix, 272.

[79] München. med. Wchnschr., 1912, lix, 806.

[80] Jour. Am. Med. Assn., 1916, lxvi, 400.

[81] Ztschr. f. Immunitätsf., orig., 1912, xii, 241.

[82] Jour. Am. Med. Assn., 1912, lix, 1236.

[83] Berl. klin. Wchnschr., 1910, xlvii, 517, 1928.

[84] München. med. Wchnschr., 1910, lvii, 1451; 1983. 1911, lviii, 138.

These examples, and they might be multiplied many times, represent a group of morbid conditions which have received most study up to the present time. A careful comparison of the symptoms following an injection of foreign protein in the sensitized man with those seen in various animals during anaphylactic shock shows a close similarity. The multiplicity of symptoms is greater in man than in any other one animal. But even typical serum disease has been observed in calves by Beclere, Chambon, and Menard,[87] and in rabbits we have noticed enlargement of the lymph nodes with subcutaneous edema from the sixth to the tenth day after intravenous injection of large quantities of horse serum.

Besides this similarity between the symptoms in man and animals there is a close analogy between the development of specific immune bodies in the two species. This was especially emphasized in considering serum disease, and the same type of immune bodies has been shown to exist in the spontaneously sensitized individual.

Precipitins to cow's milk have been found in the serum of nurslings by Kleinschmidt, and Clowes[88] and Koessler[89] have noted precipitins for pollen in the serum of hay fever patients. Bruck[90] was able to sensitize guinea-pigs passively to pig serum with the blood of a patient who developed violent gastro-intestinal spasm and urticaria after eating pork. Similar results were obtained by Schloss[91] with the serum of his patient, who was sensitive to egg-white, and by Koessler with the serum from cases of hay fever.

The specific skin sensitiveness which is obtained in immune rabbits and guinea-pigs, and which is a characteristic of the artificial sensitization by antitoxic sera in the human being, is an especially prominent feature of the spontaneously sensitized.

The application of minute quantities of specific protein to the skin of such a patient causes a severe local urticaria and erythema, and just as the skin reaction has been employed to estimate the degree and persistence of sensitization in people subjected to one or two injections of antitoxic sera, so it has been used now quite extensively by Schloss, Talbot, Koessler, Cooke,[92] Goodale[93] and others to determine the protein to which these people may be sensitive. There can be no doubt that the skin sensitiveness is solely dependent upon the introduction of protein, for Schloss obtained cutaneous reactions in his case of egg idiosyncrasy with pure ovamucin, ovoglobulin, ovoalbumin, and ovomucoid. We, too, have obtained striking skin reactions with chemically pure phaseolin, prepared from beans and kindly sent us by Profs. Mendel and Osborne, of Yale.

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[85] München. med. Wchnschr., 1912, lix, 401; 1641.

[86] Ibid., 1914, lxi, 543.

[87] Ann. d. l'Inst. Pasteur: 1896, x, 567.

[88] Proc. Soc. Exp. Biol. and Med., 1913, x, 69.

[89] Forchheimer's Therapeutsis, 1914, v, 671.

[90] Arch. f. Dermat., 1909, xcvi, 241.

[91] Loc cit.

[92] Laryngoscope, February, 1915.

[93] Boston Med. and Surg. Jour., 1914, clxx, 837.

An analysis of the conditions of sensitiveness in these patients, however, shows that they differ in some respects from the artificially sensitized. In the first place the degree of hypersusceptibility is generally much greater than is ever reported in the artificially sensitized. In the second place the sensitization is usually multiple, and in the third place the method of sensitization is problematical.

Not only is the increased susceptibility seen in the general violent reactions following subcutaneous and intravenous injections of the specific proteins which may be so great that a subcutaneous injection of 1 c.c. of 1 to 1000 dilution of serum, or as stated by Koessler, 1 c.c. of a 1 to 50,000,000 dilution of pollen extract will bring about general urticaria and asthma, but it is also noticeable in the response of the skin and mucous surfaces. Patients artificially sensitized with horse serum rarely develop horse asthma, though such a thing is possible, for Sewall[94] reports an attack of rabbit asthma in a man who has been injected with rabbit serum. Mere contact with horses will not produce anaphylactic symptoms in guinea-pigs sensitized to horse serum, though instillation of serum into the nose or trachea will do so. Even rarer are gastro-intestinal symptoms following ingestion of proteins to which either man or animal has been actively and artificially sensitized. In the sensitized guinea-pig numerous observers have attempted to produce shock by way of the gastro-intestinal tract, but all have met with complete failures. We have seen, on the other hand, that gastro-intestinal symptoms are common in the individual with spontaneous sensitization. The relative susceptibility of the skin and mucous membranes in these individuals may, however, vary greatly, and though the inhalation or intradermic injection of foreign protein may bring about general urticaria and asthma, ingestion of the same protein may be absolutely harmless and without the slightest effect upon the gastro-intestinal mucosa. Thus one of our asthmatics whose skin was highly sensitive to sheep serum and who on several occasions develped urticaria and asthma after a minute subcutaneous injection, could take by mouth large quantities of sheep serum without the slightest gastro-intestinal symptoms.

The second point of difference, namely, the multiple sensitiveness, is very difficult to interpret. Whereas the artificial sensitization of both man and animals is within limits specific, these patients frequently give a history not only of idiosyncrasies to more than one substance, but as most observers who have studied their skin reactions have noted, give positive skin tests to several different proteins. In the patients whom Dr. Rackamann and I have investigated, this has been quite regularly noted. We have found, however, that the skin reaction and occasionally the general reaction is limited to certain groups of proteins. Patients can thus be roughly classified as those who react to the sera of animals, those who react to eggs or the sera of fowls, those who react to the extract of shellfish, and those that react to the protein of plants. Occasionally the same individual may show sensitization to two or three groups, but, as a rule, it is confined to one. These reactions, too, we have found are not limited solely to abnormal patients, since in a long series of apparently healthy individuals we have found two or three who show skin sensitiveness to two or more foreign proteins.

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[94] Arch. Int. Med., 1914, viii, 856.

It is, of course, possible, as was shown early by Rosenau and Anderson, to sensitize the guinea-pig to at least three different proteins, to each one of which the animal will react specifically, and one might suppose the same could easily happen to human beings once the path to sensitization was open. Besides this it is known, that only within certain limits is the anaphylactic reaction specific inasmuch as guinea-pigs highly immune to the serum of one animal will show mild anaphylactic symptoms when injected with the serum of a closely allied species. This is especially true for man and ape, horse and ass, while Wells and Osborne[95] have shown that the same is true of plant proteins, for an interanaphylactic reaction takes place between chemically pure gliadin from wheat and hordein from barley.

The wide range of sensitiveness, however, and the great unlikelihood that the person might come in contact with many of these proteins, makes it very doubtful whether this, which is accepted by some as an explanation, is correct.

A second possibility, namely, that the sensitization is nonspecific, must be considered. It is known that when native proteins are heated or brought into contact with alkalies or other chemical agents their physical properties are injured and they no longer give specific biological reactions. References has already been made to the effect that iodin and salvarsan may have. The protein under these circumstances is said to be denatured. By this process of denaturizing, Landsteiner and Prasek[96] were able to destroy partially the specific precipitin reaction to horse serum. It is possible to conceive, therefore, that during a natural process of sensitization, through whatever route, the native protein is denatured, and when it comes in contact with the cells and tissue juices, produces a nonspecific sensitization. This might be especially true if the protein enters the body by way of the gastro-intestinal tract, and is accepted as the explanation by Otto and Hoefer.[97]

Although the mode of sensitization might seem at first glance easy to explain, there are certain factors involved that really make its interpretation very difficult. The paths open for such a sensitization are, of course, numerous. Wounds of the skin and mucous membranes might readily be held responsible, and even through the unbroken mucous membrane sensitization may be accomplished in animals. The history of many of these cases of spontaneous sensitization suggests that the process has taken place by one of these routes. But such an explanation is not applicable to all cases, and cannot account for the fact that an infant shows violent symptoms the first time it is fed an egg.

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[95] Jour. Inf. Dis., 1913, xii, 341.

[96] Ztschr. f. Immunitätsf., orig., 1914, xx, 211.

[97] Ztschr. f. Hyg. u. Infektionskrankh., 1915, lxxx, 1.

The history of idiosyncrasies in certain families, such as the tendency to asthma or hay fever, or the susceptibility to certain foods, has long been recognized as very common. Cooke obtained a history of some idiosyncrasies in the immediate families of 129, or 63.8 per cent., of 205 cases of hay fever, and everyone who has written on the subject of asthma draws attention to the familial tendency, Lesné and Richet report the occurrence of egg sensitiveness through three generations. Inheritance must, therefore, be considered as a possibility. Immunity to certain poisons may be transmitted from mother to offspring, and it has been definitely shown by Rosenau and Anderson,[98] Gay and Southard,[99] and by Lewis[100] that the same is true of hypersensitiveness to horse serum in guinea-pigs. Hypothetically this may take place in one of three different ways: as true inheritance through the germ plasm of the cells, either of the father or mother; second, by direct influence of the immunizing agent that affects the mother, upon the cells of the fetus, which would produce active immunity in the child. Third, by passive transference of the immune bodies from mother to fetus by way of the blood or milk.

It was shown by Ehrlich[101] in studying the transmission of abrin and ricin immunity in mice that this is conferred only by the mother, and that even when the mother is immunized during pregnancy the immunity in the offspring lasts but a few weeks. He concluded that this was, therefore, in no sense of the word a true inheritance, but the passive transference to the fetus or child of immunity through the blood or milk of the mother. The immunity is not transmitted to the second generation. The same principle has been established in the transference of other forms of immunity and in experimental anaphylaxis. Groer and Kassovitz[102] have concluded from a recent study that the antitoxin for diphtheria, which Schick showed was present in the blood and tissues of many human beings was transmitted passively from mother to infant through the placenta. The facts so far collected regarding the familial tendency of idiosyncrasy to foreign protein

[98] Loc. cit.

[99] Loc. cit.

[100] Jour. Exp. Med., 1908, x, 1; 608.

[101] Ztschr. f. Hyg. u. Infectionskrankh., 1892, xii, 183.

[102] Ztschr. f. Immunitätsf., orig., 1914, xxiii, 108.

do not accord absolutely with those observed in experimental transference of immunity and anaphylaxis from mother to offspring. In the first place, sensitization in man is not transient but often of years' duration. In the second place it may occur through four generations, and in the third place it is often noticeable principally or solely, as occurred in the extraordinary family described by Laroche, Richet and St. Girons,[103] in the male members. And finally, the sensitization may not always be to the same protein. In at least one family which we studied the father was sensitive to horse serum and the son to egg-white. If inheritance is a factor, therefore, it cannot be by means of passive transfer from mother to infant, but in some instances, at least, may be a true inheritance of cell characteristics derived either from the father or mother. The whole problem, since it is one of greatest importance, needs careful study, but one is almost inclined to suggest that occasionally sensitization toward foreign protein may be an inherited characteristic of the cell plasm and often not highly specific in character. Whether this is dependent upon the presence of true antibodies to the foreign protein or ferments, as Abderhalden and others have suggested, it is impossible to say. That receptors in the sense of Ehrlich for sheep cells may reside in the organs of such species as lobsters, crabs, chickens, and dogs, has been shown by Amako,[104] and more important still is the demonstration of von Dungern and Hirschfeld[105] that the isoagglutinins are inherited and transmitted strictly according to Mendelian law.[106]

The high degree of susceptibility in some people with spontaneous sensitiveness, the multiplicity or lack of specificity of sensitization, and the distinct tendency for it to occur in families differentiate these individuals from the artificially sensitized, and suggest that there is some unknown factor here which is absent in men and animals subjected to artificial sensitization.

The introduction of foreign protein, however, results in essentially the same reaction in both instances and individuals in this state of spontaneous sensitization suffering from the effects of contact with protein ordinarily harmless must clearly be differentiated from the normal person who becomes ill from the absorption of one of the poisonous products which may through various means be split off from the protein molecule.

Undoubtedly certain violent intoxications in man are caused by the entrance into the body of these toxic products of protein digestion, and it is possible that they may give rise to symptoms which resemble the true anaphylactic shock. The rupture into the peritoneum of an echinococcus cyst is frequently attended by violent symptoms of collapse which Weinberg and Ciuca[107] have ascribed to anaphylactic shock. But as it is difficult to sensitize animals to the fluid of echinococcus cysts, or to show that animals or men carrying echinococcus cysts are sensitized to the fluid, and since the fluid itself is toxic, Graetz[108] concludes that the symptoms after rupture are not due to anaphylaxis but to the absorption from the peritoneum of toxic products split from the protein of the cyst.

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[103] Gaz. d. hôp., 1912, lxxxv, 1969.

[104] Ztschr. f. Immunitätsf., orig., 1914, xxii, 641.

[105] Ibid., 1909–10, iv, 531.

[106] Since this lecture was delivered the important work of Cooke (Jour. Immun., 1916, i, 201) has been published. He has shown from a clinical study of the family history of a large group of patients suffering from such evidences of protein sensitization as hay fever and susceptibilities to certain foods, that sensitization affects members of families in a proportion which closely approximates the theoretical figures of the Mendelian law and suggests that sensitization is inherited in the strict sense and is transmitted as a dominant characteristic.

The investigations of Whipple[109] and of Murphy and Brooks[110] upon the acute poisoning in dogs whose duodenum has been closed off in a loop, have shown that the symptoms are due to a toxin absorbed through the duodenal mucosa, and recently Whipple, Rodenbaugh, and Kilgore[111] have been able to isolate this toxin and show, as they believe, that it is proteose. It may be, therefore, that the acute collapse and toxic symptoms that accompany some of the severe gastro-intestinal disturbances are caused by the absorption of proteoses or such substances as histamin. These poisonous substances may be taken into the gastro-intestinal tract with the food, especially if it is spoiled, or they may be present there already. Such attacks of food poisoning are perfectly familiar, but it is questionable whether they result in sensitization, and they should not be confused with anaphylaxis.

So far our attention has been concentrated wholly upon the susceptibility of man to the proteins of animals and the higher plants or their split products, but it is necessary now to refer, at least briefly, to a somewhat different form of susceptibility but one of great importance, namely, "allergy" or changed reactivity or hypersusceptibility to infection.

The principle is beautifully illustrated by the classical experiments of von Pirquet on vaccination. Cutaneous inoculation of the normal individual by the virus of vaccinia results in the appearance after an interval of nine to twelve days of the typical skin lesion or local vaccinia, the normal reaction. Vaccination of a person recently immunized to cowpox shows within twenty-four hours the appearance of a small vesicle surrounded by a red areole which rapidly fades, and revaccination after several years results in a positive "take" which, however, appears early on the sixth or seventh day instead of the ninth or twelfth day as it does in the normal individual.

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[107] Compt. rend. Soc. de biol., 1913, lxxiv, 1318; 1914, lxxvi, 340.
[108] Zeit. f. Immunitätsf., orig., 1912, xv, 60.
[109] Jour. Exp. Med., 1913, xvii, 286, 307; 1914, xix, 166.
[110] Arch. Int. Med., 1915, xv, 392.
[111] Jour. Exp. Med., 1916, xxiii, 123.

The similarity to the normal immediate and the accelerated reactions on inoculation and reinoculation of horse serum is very striking, and was immediately apparent to von Pirquet.

The relationship which anaphylaxis bears to this broad field of immunity and susceptibility, and the part which the poisonous products of protein digestion may have in causing the symptoms of infections, such as fever, was thoroughly discussed by Dr. Vaughan two years ago, and I shall therefore confine myself to one phase of the subject which will still repay study.

A method of studying the allergy to infection in man which has been developed within the last few years is the altered local reaction to the conjunctival, subcutaneous, or intracutaneous injection of bacteria or their extracts. The reaction of the conjunctiva and the skin of tuberculous patients to tuberculin is perfectly familiar. Similar specific reactions have been obtained with the extracts of bodies of the infecting bacteria in such disease as glanders, typhoid fever, syphilis, the trichophytic infections, and lobar pneumonia. In general it may be said that the response to the injection of these organisms or their extracts appears either during the course of the infection or after recovery of the individual. The tuberculin reaction, according to most observers, appears in animals fifteen to twenty days after infection by the tubercle bacillus. The typhoidin reaction of Gay can be obtained many years after recovery from typhoid fever. Müller, Gachtgens, and Aoki[112] who have studied the development of the mallein reaction in glanders in horses, state that the skin test may give a positive result on the fourth or fifth day after infection, and Weil,[113] who has recently described a cutaneous reaction obtained in a certain proportion of cases of pneumonia, when the autolysates of pneumococci are employed, states that the reaction first appears after the crisis.

The pathology of all these reactions is very similar, and though the histology of the lesion has only been studied extensively in tuberculosis, the few observations which have been made of the other reactions indicate that they resemble one another very closely, and consist principally in the infiltration of the subcutaneous tissues by mononuclear cells which are collected about bloodvessels. Unlike the reactions obtained with animal and vegetable proteins in sensitized individuals these reactions do not come on within the first few hours after inoculation, but make their appearance first in twenty to forty-eight hours. The tuberculin reaction may be delayed for two or three days and the luetin reaction for ten days to three weeks.

It is possible that similar local forms of allergy occur spontaneously during the course of many diseases. In the cases of chronic infections by the Streptococcus viridans the cutaneous hemorrhages and painful nodules have been supposed to result from emboli to the skin, but Dr. Lamb, in studying a few of these lesions in serial section, has been unable to find thrombosed vessels. The histological picture is again not unlike that seen in the tuberculin reaction. Quite similar is the change in the glomeruli of the kidney so common in these cases and so unlike the acute suppurative processes usually encountered in acute infections, that it is possible it may represent an allergic reaction toward the infecting organism.

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[112] Ztschr. f. Immunitätsf., orig., 1910, viii, 326.

[113] Jour. Exp. Med., 1916, xxiii, 11.

Faber[114] has recently shown that a previous injection of streptococci into the joint of a rabbit will alter the local resistance of the joint in such a way that intravenous injections of that type of streptococci which in normal animals rarely, if ever, affects the joints, invariably produces in the treated animals a localized infection of the joints in these animals. This local allergy seems, too, to be specific. Finally, one may cite the transition of an acute local infection to a chronic local inflammation as a beautiful example of allergy or changed reactivity to an infecting organism. It is worthy of notice, too, that many of these local allergic processes are associated in human beings with the appearance of mononuclear cells. In rabbits the polymorphonuclear leukocytes predominate both in the tuberculin reaction and in that obtained with animal proteins.

During the artificial immunization of both man and animal by repeated subcutaneous injections of bacteria or their extracts both local and general reactions occur which must be interpreted as an evidence of allergy. It is generally recognized that severe local and general reactions are much more likely to occur in patients who have had typhoid fever or who have been subjected to previous inoculation than in normal individuals, and that the local or general reaction in normal persons is more likely to be severe following the second or third inoculation than after the first. Nichols[115] states that severe local reaction occurs in 50 per cent. of cases after repeated inoculation. In very rare instances the general reactions following large injections of bacterial vaccines spaced at long intervals are immediately followed by alarming collapse, swelling of the face, dyspnea, and suppression of urine a condition not unlike anaphylactic shock.

Indeed many of these condition have been ascribed to sensitization, likened to anaphylaxis and accepted as such. Bacterial bodies contain nucleoproteins, the proportion of nitrogen varying in different bacteria from 8 to 10 per cent., and it cannot be doubted that it is possible to produce anaphylaxis with bacteria or their products though the primary toxicity of these suspensions and extracts is often so great that the results of many experimenters leaves one in doubt as to whether the effect of injection is really

[114] Jour. Exp. Med., 1915, xxii, 615.

[115] Ibid., 780.

that of anaphylactic shock or some other form of rapid intoxication. In working with bacteria the results are always complicated by the presence of poisonous substances, whatever their origin, and until it is possible to obtain from bacterial bodies proteins free from the toxic split products, or substances developed from bacterial growth, it will be difficult to determine what part the true protein sensitization and the anaphylactic reaction plays in susceptibility and infection.

Even the extensive studies upon tuberculosis have not completely explained the reactions which Koch's O. T. tuberculin, which is a glycerin broth filtrate, calls forth. In general the reactions produced in the tuberculous individual differ very slightly from those obtained with bacillus emulsion or extracts rich in protein, but with the latter animals may be readily sensitized, while with the former, though such sensitization has been accomplished, it is with great difficulty, and the reactions according to Lewis[116] are dependent upon the protein in the broth rather than in the extract from the bacilli. Though Baldwin[117] showed that animals may be sensitized with tuberculoprotein as with other bacterial proteins, most workers have failed to sensitize guinea-pigs passively with the serum of tuberculous patients or animals. Austrian[118] has shown that such a thing is possible if tuberculoprotein instead of Koch's O. T. tuberculin is used as antigen. Animals actively sensitized to tuberculoprotein may give a very faint skin reaction to O. T. tuberculin, though the infected animals, of course, react strongly. In fine, the skin reaction and the general reaction to O. T. tuberculin seem to depend upon the presence in the body of an active tuberculous focus, and Bail[119] in transplanting tuberculous tissue from a tuberculous to a normal animal found that the reaction after the injection of tuberculin always takes place in the tuberculous tissue. It is evident, therefore, that though the reaction in the tuberculous patient or animal is the same whether tuberculoprotein or O. T. tuberculin is employed, the anaphylactic reactions differ greatly and cannot be obtained with the latter.

To what extent the forms of allergy, such as the diagnostic skin reaction, in other infectious processes are dependent upon protein sensitization, and can thus be accredited to true anaphylaxis, is uncertain, but before sweeping conclusions can be made upon the identity of allergy and anaphylaxis much careful experimental work is necessary.

The analogy is very close, however, and since one of the striking features in infectious processes is the response on the part of the body by exudation and proliferation of cells, namely, an inflammation, it is important to determine whether similar processes accompany or follow anaphylactic reaction to simple proteins. The characteristic result of acute shock in guinea-pigs is the appearance of hemorrhages. But the guinea-pig that has recovered from a single shock shows no permanent trace of these lesions. Repeated injections of serum made subcutaneously in rabbits, on the other hand, give rise to edema, hemorrhage, and necrosis, as was pointed out by Arthus, and the lesion is characterized according to Schlecht and Schwenke[120] by an exudation of mononuclear cells and eosinophilic leukocytes. Friedberger and Mita[121] and Ishioka[122] showed, too, that horse serum sprayed into the trachea of sensitized guinea-pigs produced a cellular type of pneumonia, the exudate into the alveoli being rich in mononuclear cells and eosinophiles. We[123] have found that repeated intravenous injections of horse serum and egg-white in sensitized guinea-pigs, rabbits, dogs, and cats brought about focal necroses in the liver, kidney, and heart muscle which was followed by an exudation of mononuclear cells. In over 80 per cent. of the animals changes were found in the kidneys which were often so extensive that they led to an advanced form of nephritis.

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[116] Arch. Int. Med., 1909, iv, 528.

[117] Jour. Med. Research, 1910, xxiii, 189.

[118] Jour. Exp. Med., 1912, xx, 149. Bull. Johns Hopkins Hospital, 1913, xxiv, 280.

[119] Ztschr. f. Immunitätsf., orig., 1911–12, xii, 451.

Though it would not be justifiable to apply the results of such experiments to disease in man, it is interesting to note that one of our patients who showed spontaneous sensitiveness to several proteins from plants, and especially to phaseolin, and who had had several violent attacks of asthma, urticaria, and diarrhea after eating beans, developed a pronounced and persistent albuminuria and cylindruria following such an attack one year ago. Undoubtedly infection is the most important factor in the cause of nephritis in men, but such observations suggest that the progressive process in the kidney may depend upon an allergy or altered susceptibility of this tissue towards the bacterial proteins.

It is known that about 10 per cent. of patients with serum sickness have a mild degree of albuminuria and show both hyaline and granular casts in the urine, and it was, therefore, with much interest that Dr. Rackemann and I studied the functional activity of the kidney during the course of this disease. Most of the patients have developed their serum sickness after the use of large amounts of antipneumococcus serum, which Dr. Cole has kindly furnished us for the treatment of pneumonia caused by the pneumococcus type I. In this study attention has been paid especially to the excretion of phenolsulphonephthalein, water, and sodium chloride. The nitrogen metabolism is so much disturbed during and after an attack of pneumonia that little significance can be attached to the changes in the total non-protein nitrogen of the blood. The coefficient of urea excretion, however, employed by Ambard has been studied by the recent modification in technic described by McLean,[124] and we have not found that this is greatly modified during serum sickness. The excretion of chlorides and water, on the other hand, is often profoundly affected. The changes that take place in the elimination of salt and water during convalescence from an attack of pneumonia, that has not had serum are as follows: During the attack the excretion of water is low and the chlorides are eliminated in small amounts and low concentration. Shortly after the attack the retained chlorides are excreted in excess of the intake and in high concentrations, but on a fixed water and salt intake soon come to a normal balance. We have not found that this course is materially interfered with by such febrile complications as empyema. In the serum sickness that may follow the use of antipneumococcus serum, and in one case after the intraspinous injection of antimeningococcus serum, the ordinary course of the elimination of water and sodium chloride is greatly disturbed. With the onset of serum disease the excretion of water diminishes rapidly and with it the elimination of sodium chloride. One important point, too, is that the patient is unable to concentrate the sodium chloride, which may fall below 0.2 per cent., a very low figure. The excretion of phthalein is in a few cases slightly affected as well, and with the appearance of albumin and casts in the urine and the development of edema, the patient present a clinical picture very closely resembling a mild case of nephritis, of the salt retention type. Sufficient studies have not been made to determine whether this salt retention is in the blood or tissues, but at all events it is usually accompanied by edema. These alterations, so far as we have observed them, are purely transitory and with the subsidence of the attack the patient and the renal function return to a normal state.

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[120] Deut. Arch. f. klin. Med., 1912, cviii, 405.

[121] Deutsch. Med. Wchnschr., 1911, xxxvii, 481.

[122] Deutsch. Arch. f. klin. Med., 1912, cvii, 500.

[123] Jour. Exp. Med., 1913, xviii, 678; 1915, xxii, 793. Arch. Int. med., 1915, xv, 1079.

Such studies are designed primarily to throw some light upon the possible importance of repeated anaphylactic shocks in the spontaneously and highly sensitized individual, and it would be the greatest mistake and misfortune at the present time if they were allowed to have any bearing on the use of antitoxic and antibacterial sera. The concentrated diphtheria antitoxin, such as is employed, now rarely produces serum disease or sensitizes sufficiently highly to make a second dose, particularly if it is given subcutaneously, in the least dangerous, and it is only to the spontaneously sensitive who react to the first injection that harm is likely to come.

To prevent accidents in such unexpected instances, especially if large quantities of serum are given intravenously, a preliminary intracutaneous injection of 0.1 to 0.01 c.c. of serum should be made to determine whether or not the patient is spontaneously sensitive to the serum which is to be employed.

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[124] Jour. Exp. Med., 1915, xxii, 212.

Though it would be interesting to recount the methods which have been employed to desensitize both artificially and spontaneously sensitized individuals, this important problem in therapeutics must be left, since there is no time to do it justice, and in conclusion I shall point out the conditions which such methods must combat.

The injection of foreign proteins in man brings about the same condition of hypersensitiveness toward subsequent injections that it does in animals.

Certain individuals may show spontaneous hypersusceptibility to one of several foreign proteins. That these people differ from the artificially sensitized, in that their susceptibility is very great, is shown toward several different proteins, and has a tendency to occur in families. And, finally, that this state is associated with and directly responsible for some well-defined pathological conditions.

THE SYMPTOMS AND PHYSICAL SIGNS RESULTING FROM WOUNDS OF THE CHEST.[1]

By C. P. Howard, M.D.,
IOWA CITY, IOWA.

From August 7 to November 1, 1915, there were admitted 3039 to the hospital to which the writer was attached; of these 1315 were sick and 1724 wounded; of the latter, 107 (6 per cent.) received either a gunshot wound or shell wound of the thorax; 20 cases were evacuated too rapidly to permit of a physical examination of the chest. This leaves 87 cases for purposes of analysis.

Forty-five were the result of gunshot wounds, and of these 41 penetrated the thoracic cavity; the remaining 4 were merely wounds of the parietal wall without obvious penetration of the pleural cavity.

Forty-two were the result of shell wounds of some kind, as high explosive, shrapnel, trench mortar, or hand grenades. Of these, 28 had certainly penetrated the chest wall and 14 had apparently not, though 1 at least had caused a fracture of a rib which had lacerated the pleural cavity.

These cases we shall divide into four groups for purposes of description and consideration.

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[1] I wish to express my appreciation to Col. Birkett, Lt. Cols. Elder and McCrae, Majors Hill and Archibald and the other officers of No. 3, Canadian General Hospital, for the opportunity to see the cases and for permission to publish them.

Group 1. Fifteen patients presented no abnormality in the lungs or pleuræ at the time of the examination. That is to say, 17.2 per cent. of wounds of the chest revealed no injury to lung or pleura a few days after the receipt of the injury, and that in spite of the fact that of these 6 were penetrating gunshot wounds and 1 penetrating shell wound. The remaining 8 had only affected the parietal wall.

Group II. A very interesting group of 6 cases comprised 4 cases of pneumonia and 2 of serous pleurisy with effusion. The 4 pneumonias all resulted from shrapnel, 2 of which were penetrating wounds. Further, what was of special interest in 2 cases, the involvement was on the side opposite to the wound. A third case was a double pneumonia associated with paralysis of the vocal cord from a missile lodging in the upper right chest behind the first rib, and was possibly originally an aspiration pneumonia. The fourth pneumonia patient had only a small shrapnel wound of the thorax, but was buried in a trench for some time and consequently much bruised about the thorax. One of the pleurisy, with effusion, cases had an accompanying pneumonic consolidation of the lung resulting from a non-penetrating gunshot wound of the opposite side. The other case was a simple serous effusion the result of a non-penetrating shell wound of the same side.

Group III. This includes one case of mediastinitis, resulting from a rifle bullet lodging in the anterior mediastinum. The only symptoms complained of were pain referred to the right side of the neck over the upper and outer border of the trapezius muscle and slight dysphagia. On inspection there was a marked area of ecchymosis over the manubrium, but, of course, as yet, no fulness of the superficial veins. There was in addition a non-fluctuating elevated tender area beneath the discolored skin from the subcutaneous hemorrhage. There was a definite area of dulness corresponding to the anterior mediastinum, reaching above to the upper margin of the manubrium; below merging with the heart dulness, extending to the right about 1 cm. beyond the sternal border and to the left just to the sternal border. On auscultation over the manubrium and raising the patient's arms above his head there was a well-marked grating friction, a sign described by Perez[2] and reported by the writer[3] in other cases of mediastinitis. A skiagram revealed a sharply pointed bullet slightly more than one inch in length lying apex downward behind the manubrium to the right of the midline one inch from the surface.

Group IV. This group comprises the hemothorax cases which for purposes of discussion have been further subdivided into the infected and sterile.

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[2] Brit. Med. Jour., 1896, i, 82.

[3] C. P. Howard, Johns Hopkins Hosp. Bull., 1915, xxvi, 140.

A. *Infected Hemothorax.* Of the 65 cases, 9 were definitely infected (13.8 per cent.). This is a somewhat lower percentage than that given by Col. Sir John Rose Bradford[4] in his series in which 25 per cent. of 328 cases were infected. Hale White[5] found only 10 per cent. of the cases in his base-hospital experience in England with evidence of infection of the fluid.

As to the nature of the wounds, 4 were penetrating gunshot wounds, 4 were penetrating shell wounds, and 1 was a non-penetrating shell wound which had caused a fractured rib, a spicule of which had lacerated the pleura and was to all intents and purposes a penetrating chest wound. The infective organism was one of the gas bacillus group in 1 case, B. tetani 1 case, pneumoccus 1 case, streptococcus 1 case, Streptococcus and Staphylococcus aureus one case, and a large unidentified bacillus (recovered on three separate aspirations) 1 case. In the remaining 3 no cultures were made.

Cough, hemoptysis, pain, and dyspnea were present in about the same proportion as in the next group, under which these symptoms will be discussed in detail.

As one might expect, the temperature range was higher in this group than in the non-infected cases, and not uncommonly ran a more or less continuous curve of 103° to 104° F. This fever curve taken in conjunction with the rapid pulse (120 to 140) and a marked tendency to polypnea (28 to 40) would always suggest the chart of ordinary acute lobar pneumonia.

In 2 cases the infection lay dormant for ten days and eighteen days respectively. In the first of these cases a penetrating shrapnel wound was received on September 25; an exploratory aspiration on October 1 revealed a bloody fluid, smears and cultures from which were negative for organisms; a second aspiration on October 5 revealed a number of organisms of the "gas-bacillus group;" a third aspiration on October 7 showed the same organism, though in smaller numbers. The second case received a penetrating gunshot wound on October 13 and ran a normal temperature, pulse, and temperature curve until October 31, when there was a sudden rise in all three (temperature, 104.4°; pulse, 120; respiration, 28), and an exploratory puncture revealed a large bacillus morphologically resembling one of the gas bacillus group, but which grew aërobically as well as anaërobically, did not produce gas, and was unidentified, but probably belonged to the group of diphtheroids found by others in this war; that it was the cause of the infection of the pleural exudate cannot be doubted, as it was found alone on three separate aspirations.

Physical Signs: The physical signs in this group differed in no way from those of the sterile cases. We never found the two signs of anaërobic bacillus infection described by Bradford, namely, a rapid displacement of the heart and a "cracked-pot" percussion note from the rapid development of gas within the pleura.

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[4] Brit. Jour. Surg., 1915, iii, 247.

[5] Lancet, 1915, ii, 1233.

Only 2 of the cases showed definite signs of pneumothorax, while in a third air and pus could be seen and heard sucking in and out of a large wound in the upper back, though none of the characteristic signs of pneumothorax could be detected, but merely those of an extensive fluid exudate. This case interested me much at the time. West[6] reports 2 cases with large wounds of the chest in which the lung did not collapse, though no adhesions were present, and in which there were no signs of pneumothorax. All of us have noted the absence of signs of pneumothorax after thoracotomy for a recent empyema. On the other hand if the empyema be of long standing and firm adhesions have formed, causing pocketing of air and pus, well-marked signs of pneumothorax may be present, as in a case seen recently in the surgical clinic (University Hospital, No. 2609). While infection should be suspected in every case which is not progressing favorably after the fourth day, it cannot be diagnosed on clinical symptoms and signs alone. An exploratory aspiration and a bacteriological examination (both smears and cultures) should be made in all suspicious cases.

As regards treatment, in 4 of the cases a thoracotomy was done, as a result of which 2 were discharged well, 1 improved, and 1 died. One case which was drained at a casualty clearing station by inserting two rubber drainage tubes between the eighth and ninth ribs in the posterior axillary line, died five days later under our care. One case was merely aspirated and was discharged improved, but whether or not he subsequently required more radical treatment is not known. In 3 cases no surgical procedures were instituted: in 1 case because a coexisting tetanus caused death; in 1 case because the patient was moribund upon admission; the third was evacuated to England at the patient's request in an apparently hopeless condition, owing to the existence of a complete paraplegia of the lower extremities

One striking feature of the cases in which a thoracotomy was performed was, in spite of the promptness of the surgical interference, the slowness of the convalescence owing to the marked tendency in these cases to the formation of adhesions and the consequent pocketing of pus that occurred.

B. *Sterile Hemothorax.* This was by far the largest group, comprising as it did 56 patients. Thirty-one were the result of gunshot wounds, of which all but one had penetrated the chest cavity. In 25 shrapnel, hand grenades, or some form of shell was the cause of the wound, 20 of which had obviously penetrated the thoracic cavity; in the remaining 5 no penetration wound was demonstrable, and the hemorrhage must have resulted from laceration of the intercostal arteries or severe contusion of the lung itself.

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[6] Emerson, Johns Hopkins Hosp. Reports: 1913, xi, 375.

The four chief symptoms were cough, hemoptysis, dyspnea, and pain in the chest.

Cough was a most constant symptom, being present in 41 cases, absent in 9, and not noted in 6. In other words, it was present in 82 per cent. of cases in which a definite note was made. For the most part it was the characteristic short, sharp, dry cough of an ordinary pleurisy. Apart from these cases, in which a definite hemoptysis occurred, sputum was strikingly absent

Hemoptysis was also a very constant symptom, being present in 39 cases, absent in 7, and not noted in 10. In other words, in 85 per cent. of the cases blood was expectorated. This varied from a few mouthfuls immediately after the reception of the wound to a more prolonged and repeated hemoptysis persisting in some cases for days. Of course, in the immediately fatal cases which were not seen by us very extensive external hemorrhage must occur in many cases. While hemoptysis is usually due to penetration of the lung, with laceration of a bloodvessel, Rose Bradford[7] believes it might also be due to an infarction of the lung from bruising when there is no proof that the missile had penetrated the lung substance. A fatal hemoptysis occurred only once in 1000 cases studied by this author.

Dyspnea was a somewhat less frequent symptom, occurring in 21, absent in 10 and not noted in 25. That is to say, it was present in approximately 70 per cent. of the cases. It was rarely marked and usually of short duration; even the cases with a small pneumothorax showed at the most slight respiratory embarrassment.

Pain in the chest was present in 24 cases, absent in 7, and not noted in 25. This means approximately 80 per cent. of the patients with a complete history complained of pain somewhere in the chest, usually at the site of the wound, though not infrequently in the axilla or front of the chest. It was always worse on breathing or on movement of any kind.

Fever of varying degree was noted in 47 patients, and was absent in 9 (*i. e.*, 99° or less). That is, 92 per cent. showed fever. Of these 20 patients had a temperature at one time or another of 102° F. or over, and 3 even of 104°. Another 12 had a rise to a point between 100.2° and 101.8°; and 15 between 99.2° and 99.8°. The presence of fever by no means indicated an infection of the pleura or underlying lung, and was due in these cases either to an infection of the parietes or to absorption of the blood contained in the pleural cavity, the latter being analogous to the so-called protein fever of the experimental laboratory.

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[7] Brit. Med. Jour., 1916, i, 129.

The pulse was accelerated in every one of the 56 cases (100 per cent.). In 10 cases it was markedly (120 or more per minute), in 35 moderately (90 to 119 per minute), and in 11 slightly elevated (80 to 89 per minute). This was no doubt due in part to the parietal infection, but chiefly to the physical exhaustion and shock experienced by the patient, as the pulse rapidly returned to normal after proper rest in bed and suitable nourishment. Hemorrhage itself played but a small role, and that only in a small proportion of cases.

Respirations were about normal in 43 of 54 cases (80 per cent.). They were markedly accelerated (*i. e.*, 32 or more per minute) in 12, moderately (25 to 30 per minute) in 14, and slightly (22 to 24 per minute) in 17 patients. In 13 cases the respiratory rate was normal upon coming under our observation at the base.

The physical signs were as follows: *Inspection* yielded invariably a diminished movement of the affected side; in some cases this was exaggerated by the patient's apprehension of causing pain or producing a hemorrhage. Fulness was not a constant feature except in the very extensive effusions. Two or more weeks after the wound one was not infrequently struck with the subsequent retraction of the thoracic wall more than one sees in civil life, except in cases of empyema or fibroid phthisis. This was due to the marked collapse of the lung, and according to writers in England is entirely recovered from as the lung expands from suitable exercises.

Palpation frequently reveals the characteristic crackling of subcutaneous emphysema for a considerable distance around the wound, being present in 10 of our 56 cases. This phenomenon no doubt is due to escape of air from the underlying lung, and is subsequent to a transient pneumothorax, though in only 2 of these cases were the other physical signs of air in the chest present. Of course, the diminished motion could also be detected. Tactile fremitus was diminished in the great majority of cases (90 per cent.), and in the remainder it was either normal (1 case), increased (1 case), or diminished in front and increased behind (2 cases). Increase of vocal fremitus is readily explainable by the compression of the underlying lung, and in our series, considering the other evidence of compression, was surprisingly rare.

Percussion. The note was usually dull in moderate effusions (30 cases) and of a woodeny flatness in the larger effusions (18 cases); in 8 no remark as to the quantity of the effusion was made. A tympanitic note was present in front or above the line of effusion in 4 uncomplicated cases, and was no doubt the Skodaic hyperresonance present in simple effusions above the level of fluid. In 3 other cases, however, the tympany was associated with other suspicious signs of a pneumothorax. In 8 additional cases the tympany occurred in conjunction with other more definite signs of a pneumothorax.

Rose Bradford called our attention to the frequency of an atonic relaxation of the diaphragm, so that the area of gastric tympany was found to extend unusually high on the left side; this phenomenon he does not believe to be due simply to a wound of the lung, for it only appears with hemothorax.[8] We examined for it in too few cases to express an opinion as to its value.

Auscultation. The breath sounds were, for the most part, suppressed or absent (30 cases), but in 19 other cases (39 per cent.) they were noted as bronchial over the back or above the line of effusion. This again shows the frequency and extent of compression of the lung. In 7 cases no note was made as to the character of the breath sounds. The vocal resonance, as determined by the transmission of the spoken voice sound with the aid of the stethoscope, was increased in 11 cases, diminished in 12, and normal in 1 case. In the remainder no note was made. Here again we find evidence of the frequency of compression of the lung.

The transmission of the whispered voice sounds (pectoriloquy) was only tested for in 5 cases, but was present in 4 of these.

Medium or fine moist rales were noted only seven times in spite of the frequency of compression of the lung. A pleural friction was more frequent, being present in 12 cases, in 3 of which it had the pleuropericardial character.

There were 8 cases of undoubted pneumothorax and 5 suspicious cases, and yet a metallic tinkle was heard in only 6 cases and the coin sound or "bruit d'airain" of Trousseau in 4. The Hippocratic succussion was not tested for, owing to the importance of keeping the patients as quiet as possible.

Cardiac displacement was a very constant sign, being present in 23 cases of 32 (72 per cent.) in which a note was made as to the position of the heart. We were much struck with the degree of displacement even when the effusion was relatively small in amount, and considered it to be further evidence of the probable frequency of the existence of a pneumothorax in the early stages of the thoracic injury. The greater density of the fluid as compared with that of ordinary serous effusions did not satisfactorily explain the greater displacement of the heart in these cases. The heart very slowly returned to its normal site even after the effusion had largely subsided, and in many cases the patient was sent to England with considerable cardiac displacement persisting.

Roentgen-ray Findings. In only 20 cases was a skiagram taken, first, as in the cases with a wound of exit it was unnecessary, and secondly, as we moved our patients as little as possible. In 12 of these cases the missile was located in the thorax, in 1 case it had penetrated the diaphragm, and had come to rest in the abdominal cavity. In the other 7 cases no foreign body could be found. In

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[8] J. Rose Bradford and T. R. Elliott, Brit. Jour. Surg., 1915, iii, 247.

3 cases fluid was still present when a search was made for the foreign body. In one other case a pneumothorax still existed.

Complications. In 2 cases there were undoubted signs of fluid on the two sides of the chest, and in a third there were signs of either a small effusion or a marked displacement of the posterior mediastinum and its contents.

As was noted before there were 8 cases of undoubted *pneumothorax* and 5 in which there was more than a strong suspicion. The majority of these cases were admitted within a day or two of one another after the British offensive of September 25 and 26, 1915, when the wounded were evacuated very rapidly to the base. Further, the signs of air in the chest rapidly disappeared, in several instances in twenty-four hours. The greater incidence in those seen shortly after being wounded and the rapid absorption of the air under observation lead us to believe, with all due respect to the opinion of Sir John Rose Bradford,[9] that a mild form of pneumothorax is a common occurrence and must be present in the majority of cases in which a missile has penetrated the lung. It is of interest to know that Otis[10] noted in the American Civil War not more than 6 cases in which a pneumothorax was a troublesome complication. We must admit with Rose Bradford that over an area of cutaneous emphysema the character of the percussion note may suggest the presence of a pneumothorax when none is present. Rose Bradford found only 12 cases of pneumothorax in 500 patients with wounds of the chest, and in only 5 was its presence proved. Hale White found only 2 cases of air in the pleural cavity in the 50 cases seen by him in England. Naturally the amount of air that escapes is very small if the missile be a high velocity bullet from a rifle or machine gun, and consequently is overlooked unless carefully examined for within forty-eight hours or so after the reception of the wound. Further, of course, there is seldom if ever a valvular opening such as one sees in a pneumothorax due to tuberculosis. As shown in several autopsies of the infected hemothorax group there is at once a sealing of the opening in the lung substance by fibrin, which effectually prevents further escape of air. In 1 case the fibrinous plug had been inflated like a small balloon by the air in its attempt to escape from the damaged lung. Lastly, Osler,[11] has pointed out that the metallic phenomena which are the most striking signs of air in the chest, are best heard in cases with a consolidated lung and thickened pleura. Distention, immobility, lack of vocal fremitus, hyperresonance, absence of breath sounds and displacement of viscera are the signs of a pure pneumothorax, and can readily be confounded with those signs of an extensive effusion.

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[9] Loc. cit.

[10] Med. and Surg. Hist. of War of Rebellion, Pt. I, vol. ii, 623.

[11] Practice of Medicine: 8th edition, 1912, 671.

Lobar pneumonia was present in 4 cases, all four being on the side opposite to the wound and the subsequent hemothorax. These 4 cases together with the two mentioned in Group II give a total of 6 cases in our series in which all the physical signs and symptoms of a pneumonic infection existed in the side opposite to the injury. While trauma is a well-recognized cause of pneumonia since the days of Litten, who found a history of it in 4.45 per cent., I can find no mention in the current text-books and monographs of the opposite lung being involved. It is difficult to understand the pathogenesis of a pneumonia by "contre-coup." Rose Bradford noted that the hemothorax and pneumothorax might be found in the side opposite to the wound in the chest when the bullet penetrated the lung transversely. He noted that contralateral pleurisy was commoner in the cases infected with streptococci; he further admits that pneumonic consolidation does occasionally occur in the contralateral lung[12] but never in the side of the hemothorax.

A secondary hemorrhage into the pleural cavity is an exceedingly rare event if the patient be kept completely at rest for several days after his injury. In some cases it is said to have been the cause of death when attempting to transport the patient to the base too early. In 100 autopsies reported by Henry[13] death was due to hemorrhage in only 8.

Private D. J. B., Reg. No. 16691, was admitted to our care forty-eight hours after receiving a shrapnel wound of the right chest in the third interspace anteriorly. On admission, in addition to signs of a moderate hemothorax, there were undoubted evidences of pneumothorax; four days later, during which time he had been kept strictly at rest, he became extremely pale, the pulse became very rapid and thready, and the respiration became more rapid and labored. The diagnosis lay between a virulent infection of the hemothorax, as described by us above, or a secondary hemorrhage. The whole picture was more suggestive of the latter. However, to make certain, an exploratory needle was introduced and a few cubic centimeters of blood which clotted in the syringe were removed. That the blood was clotted was proof of the recent occurrence of the hemorrhage, as the bloody exudate usually removed by aspiration or drainage shows little or no clotting *in vitro*. Further the smears and cultures were negative and the patient gradually recovered with merely supportive treatment and absolute rest.

A case of cholohemothorax has been reported by Elliott and Henry[14] from a fistula between the liver and pleura following a bullet wound.

In 3 cases there was a simple fibrinous *pericarditis*, as evidenced by the presence of a pericardial friction. In 2 of these cases the wound was in the left chest. In another patient who had received a gunshot wound of the chest, the bullet having entered at the left nipple and passed out at the right nipple, there were signs of fluid (namely, a triangular area of absolute cardiac dulness and distant heart sounds), with the subsequent development of a to-and-fro pericardial friction, all of which were very suggestive of a hemopericardium.

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[12] J. Rose Bradford and T. R. Elliott, Brit. Jour. Surg., 1915, iii, 247.

[13] Brit. Med. Jour., 1915, ii, 130.

[14] Ibid., 1916, i, 9.

In still another case there were the characteristic signs of a *pneumopericardium.* As I hope to report the case at some length in the near future, suffice it to say that the patient received a shell wound of the lower left posterior aspect of the chest; the missile must have penetrated the diaphragm as well as the pleura, with the production of a subdiaphragmatic abscess. Two weeks after the receipt of the wound he developed sudden dyspnea, rapid pulse, precordial tympany, absence of heart sounds, and the presence of a most remarkable to-and-fro churning, musical, echoing sound synchronous with the systole and diastole of the heart, and persisting upon holding the breath. Some days later, after the air was absorbed, a dry pericardial rub became audible.

Twelve cases were complicated by extensive *infection* of the tissues from wounds for the most part other than those about the chest. In 2 cases the patient nearly succumbed to a secondary hemorrhage from the invasion of one of the main arteries of the upper or lower extremity. The case of the subdiaphragmatic abscess has already been referred to.

TREATMENT. In the majority (70 per cent.) of the cases apart from absolute bed rest and a bland nutritious diet no treatment was necessary, the bloody exudate being absorbed usually at the end of fourteen days after the reception of the wound. In 3 cases, in spite of the presence of signs at the expiration of two weeks, an exploratory aspiration was negative. In 5 other cases an exploratory aspiration revealed sterile bloody fluid, but the withdrawal of a few cubic centimeters sufficed to promote absorption. In another 5 cases amounts varying from 400 to 1600 c.c. were removed. This fluid was withdrawn slowly by means of an ordinary Potain aspirator without causing any outward symptoms. It never reaccumulated. The fluid itself varied in color from an ordinary deep scarlet to a deep chocolate; it was usually thin but sometimes of a syrupy consistence, and on standing showed little or no clotting. Only in one instance was an appreciable amount of fibrin noted. The postmortem examination of one case in the setrile and in several of the infected cases readily explains the absence of clotting *in vitro,* as the visceral and parietal pleuræ were covered by thick fibrin which had evidently separated out *in vivo.* This fibrin not infrequently plugs the lumen of the needle unless a large one (preferably a trocar) be used. Upon standing a sediment of red cells in various stages of decomposition with an occasional leukocyte can be found.

Henry[15] believes that primary coagulation of the effused blood and a deposition of fibrin occur in a few hours; afterward exudation of lymph may occur which will induce secondary clotting. Denny and Minot[16] offer experimental proof that the blood remains fluid in the pleural cavity not because of any alteration of its elements but because of previous coagulation and defibrination. Following the suggestion of Colonel Sir John Rose Bradford, two cases of extensive simple hemothorax were treated by aspiration and oxygen replacement. We used a simple home-made manometer and the oxygen tank of the Clarke oxygen-ether apparatus, introducing two needles into the chest, one for aspiration and one for the oxygen to enter. An attempt was made to keep a constant pressure equal to that noted before the withdrawal of any fluid. Of course, the resultant pneumothorax persisted for two or three days, and then gradually disappeared. We see no reason why all cases could not be aspirated if this procedure be used early (let us say on the sixth or seventh day) without giving rise to secondary hemorrhage, as was experienced by the physicians of the Royal Army Medical Corps in the South African War.

PROGNOSIS. Of the 87 cases only 6 died (69 per cent.), and of these 6 cases 4 were infected hemothorax, 1 died as the result of multiple amebic abscesses of the liver with local peritonitis, and 1 from an infected bullet tract in the lung. That is to say, approximately 8 per cent. of our hemothorax series died, which approximates very closely the mortality of Rose Bradford's series. In the latter's series of about 450 cases 10 per cent. died from sepsis, 5 per cent. from hemorrhage, and others from sundry complications.

In our series 69 were discharged well (79.3 per cent.), 11 improved (12.6 per cent) and on the high road to recovery; 1 was sent to England unimproved because of a coexisting paraplegia of the lower extremities. These encouraging figures, of course, hold true for only those cases which are removed from the battle-field and are eventually evacuated to the base. Many wounds of the chest must be fatal within a short time. As to what is the proportion of these we have as yet no figures to guide us. The ultimate prognosis of wounds of the chest, according to Hale White, seems to be good, for it is not uncommon to see such cases returned to the firing line. Convalescence is necessarily slow, but the flattening of the chest almost disappears in the course of several months.

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[15] Loc. cit.

[16] Amer. Jour. Physiol., 1916, xxxix, No. 4.

SPECIFIC AND OTHER FORMS OF SPONDYLITIS.

By B. Sachs, M.D.,
NEW YORK.

(From the Neurological Service of Mt. Sinai Hospital.)

Some early forms of spondylitis constitute a No Man's Land, definitely charted by none, and vaguely claimed by all. The chronic cases belong very properly in the domain of orthopedic surgery. The incipient and more acute forms are recognized more readily by the neurologist. Traumatic spondylitis, tuberculous spondylitis, as well as those forms of carcinomatous or sarcomatous deposits in or near the vertebræ are not to be considered in this discussion.[1] Special attention is to be directed to specific spondylitis and to a senile form, which, for want of a better term, may be designated as a chronic or universal spondylitis closely allied to spondylitis deformans. I wish also to direct attention to that form of spondylitis occurring in the senile period which has been the subject of considerable study.

In the neurological division of Mt. Sinai Hospital the question of spondylitis has arisen so frequently within the last few years that a thorough examination of the spinal column has become a matter of routine. Our own experience has been opposed to that of Nonne, Oppenheim, and Lewandowski, who regard specific spondylitis as a relatively rare disease.

In his well-known monograph Nonne states that Eugene Frenkel did not discover a single case of unquestionable luetic caries during a period of thirty years as pathologist of the large hospitals of Hamburg. Leyden and Jurioux were of the opinion that a mistaken diagnosis might be made if we considered every case of caries in a specific subject necessarily syphilitic. Nonne refers to a patient who exhibited the symptoms of cervical caries one year after a specific infection. The patient died seven years later of a general tuberculosis. At the autopsy he found a tuberculous caries associated with a specific meningitis. We are all fully aware that the histological differentiation between tuberculous and syphilitic tissues is a difficult matter, and even with our present modern methods, especially with the aid given us by roentgen-ray examinations, the question cannot in every case be settled satisfactorily as to whether a given lesion be tuberculous or specific, and yet in a vast majority of the cases there are sufficient points of differentiation, some of which are brought out by a careful study of the roentgen-ray findings.

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[1] Held before the New York Neurological Society at its meeting December 7, 1915. The subject was illustrated by lantern slides and radiographic demonstrations.

Whatever the etiological factor may be the clinical symptoms are about as follows: First of all, a partial or complete immobility of some part or parts of the spinal column. In the cervical cases there is distinct rigidity of the neck and almost complete fixation of the head. In many instances there is distinct pain on pressure over the spinous processes. Among the other symptoms, in the order of their importance, we may rank radiating pains, according to the segments involved, typically root pains; slight atrophies of the muscles around the neck and shoulder girdle or of the hip and thigh muscles. There are distinct areas of altered sensibility varying from slight anesthesias to distinct hyperalgesias of the sort that we are accustomed to encounter in cases of spinal neoplasm, and for this reason, as well as for the painfulness on pressure, the differential diagnosis between spondylitis and neoplasm of the cord is to be considered. Wasting of the muscles, a paretic condition of the affected parts, and altered reflexes, either diminished, if due to involvement of the roots, or increased reflexes, associated possibly with spastic forms of palsy if the spinal cord is at all compressed, constitute a striking clinical picture.

These symptoms may, of course, be aggravated to such an extent that the patient finally presents all the symptoms of a compression myelitis. The variability of the symptoms, the exacerbation and remission, and, finally, the prompt subsidence in accord with therapeutic measures are so characteristic of all syphilitic lesions that they help to suggest the special character of these luetic forms. The suspicion of the syphilitic origin of these forms of spondylitis is confirmed by the Wassermann reaction of the blood and possibly of the spinal fluid as well as by the increased lymphocytosis and the high cell count of the cerebrospinal fluid. Furthermore, the roentgen-ray picture of specific spondylitis has none of the ear-marks of tuberculous caries. There is never any real crushing of the bone, and the changes are always much more on the periphery than in the center of the vertebræ. It is much more difficult to differentiate the roentgen-ray picture of these specific forms of spondylitis from that of other forms of chronic spondylitis, especially spondylitis deformans. Dr. Jaches, whose opinion on this subject I value most highly, hesitates to decide from the roentgen-ray findings alone whether or not a given case be luetic. If, however, the examination of the blood and spinal fluid, the roentgen-ray findings and the rapid improvement following upon specific treatment suggest the specific character of the disease, it would be straining a point not to recognize specific spondylitis as the most plausible diagnosis.

The occurrence of such forms of spondylitis in association with tabes, as I have seen in a few instances, tends to strengthen the belief in the relative frequency of this form of spondylitis.

Without wishing to burden this paper with detailed histories

I shall refer to a few cases that are entirely typical of the various forms to which I have alluded.

The patient, L. C., presented at the meeting is still under observation at the hospital.[2] He was admitted only a few weeks ago markedly paretic in the upper extremities with very limited motion of the head and with a general spinal rigidity; he also gave a history that a number of months ago, at another hospital, he was operated upon in the mid-dorsal region because of the symptoms which he presented and the radiating pains and possibly definite areas of disturbed sensation. Nothing abnormal was found. I have no fault to find with this operation, for I remember some twenty-odd years ago having caused a similar operation to be done upon a patient who presented such symptoms, and who at the time of the operation revealed nothing but a very much thickened dura and a formation of tense fibrous strands on the inner surface of the laminæ. In this same instance there was a distinct improvement in the carriage and in the general condition of the patient after the operation. In this present case no improvement was noted after the operation: the patient became worse, the affection in the cervical regions evidently becoming much more severe until he was compelled to come to the hospital for relief.

His condition on admission may be summarized briefly as follows: Rigidity of the neck; marked limitation of movement of the upper extremities; pain along the course of both brachial plexuses; exaggerated biceps and wrist-jerks; gait somewhat spastic; lively deep reflexes in lower extremities; Achilles reflexes very lively; abdominal reflexes also lively; entire vertebral column rigid, with tenderness over cervical, lumbar, and sacral spines; scar of operation over lower half of thoracic region; hyperesthesia and hyperalgesia and increased sensitiveness to cold over both lower extremities anteriorly and posteriorly from the level of the crest of the ilia. The Wassermann reaction of the blood was + + + +. The roentgen-ray findings were: "Marked degree of spondylitis in the 4th, 5th, and 6th cervical vertebræ; in the 11th and 12th thoracic and in the 1st lumbar vertebræ; an apparent diminution in size of the 5th lumbar vertebræ."

Once the specific character of the blood was determined active treatment was instituted, the patient receiving intravenous and intramuscular injections, and the result has been most gratifying, the patient at the present time being able to raise his arms and to use his hands, and has also begun to move his head quite freely.

Another patient whose disease was of special interest was A. P., aged thirty-four years, a clerk, who was admitted to Mt. Sinai Hospital on October 29, 1912. He was then married four and a half years; had no children; his wife has had no miscarriages. His family history was practically negative. According to his own statement he had acquired gonorrhea and syphilis about ten years previously. He received at that time ten mercurial injections and was given mercury by mouth. So far as he knows there were no secondaries. About eight months before admission to the hospital he had painful stiffness of the neck lasting three weeks. Four months ago the pain returned and was located in the upper part of the back and neck radiating to the collar-bone and middle of both arms. The pain was persistent, worse at night, and was aggravated by any sudden jar or rotation of the head. He also stated that during the past few weeks he had some difficulty in swallowing food, as he thought, because of some swelling in the throat. He had no fever or cough, but occasionally had some night sweats. There was no dyspnea, no bladder disturbances, and no sensory disturbances.

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[2] In February, 1916.

The patient presented a marked limitation of motion of the head in every direction. The head was practically fixed. Behind the middle of the left sternomastoid muscle, and also on the right side in the same position, there was a small, hard, nodular mass. There was marked tenderness to pressure over the upper four cervical spines, a marked prominence of the second cervical, and a slight right scoliosis in the cervical region. His gait was normal except for his modified carriage. The reflexes were normal and there were no other objective symptoms.

The swelling on both sides of the neck, the pain on pressure on both sides of the spines, pointed strongly to an involvement of the vertebræ. Shortly after admission the Wassermann reaction of the blood was positive; the cerebrospinal fluid was negative. The roentgen picture as developed by Dr. Jaches showed that the body of the fourth cervical vertebra was greatly destroyed, more markedly on the left than on the right side. The lower part of the third and the upper part of the fifth vertebræ were slightly eroded.

The patient was put on salvarsan treatment. On November 4 he was given 0.4 intraveneously; on November 15, 0.3, and on November 27, 0.4. After the first injection the pain was distinctly lessened; after the second we noticed a marked improvement, and after the last treatment the condition showed very satisfactory improvement. He was discharged from the hospital on December 4, able to move his head in every direction and entirely free of pain. He returned to the hospital for observation a number of times. A second series of roentgen-ray plates proved that the bone process was undergoing resorption.[3] If all signs do not fail us it is fair to claim that in this the wry-neck was due to syphilitic caries of the cervical vertebræ.

Resembling this very case is that of another patient, aged fifty-six years, J. R. H., who gave a distinct luetic history, and whose symptoms were not unlike those previously recorded. He complained of pain in the left shoulder radiating down the left arm; of weakness in the left upper extremity, and of pain in the back, for two months previous to admission to the hospital; also of paresthesia in the right lower extremity.

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[3] The roentgen-ray evidence of improvement in this case was most convincing.

On examination we found tenderness in the left shoulder; wasting of the muscles of the left shoulder girdle and of the left forearm; distinct wasting of the thenar and hypothenar eminences, and wasting of the interrossii. The grip of the left hand was weak. There was also hyperesthesia of the right half of the scalp and of the right upper extremity except in the hand. The Wassermann reaction of the blood and of the spinal fluid was negative, but there was distinctly increased lymphocytosis of the cerebrospinal fluid and 97 per cent. lymphocytes.

In this case again the roentgen-ray examination revealed a spondylitis of the 5th, 6th, and 7th cervical vertebræ and a very slight lesion in the third and fourth cervical. In such a case as this there may be some doubt as to whether we can positively claim that the spondylitis is of specific origin, although there is considerable temptation to put such a case as this in this category, and, indeed, it leads us to suspect that a number of the cases of generalized spondylitis of unknown origin may, on closer examination, prove to be specific.

After setting aside the specific cases of spondylitis a number of others remain, occurring in middle age both in men and in women, possibly a little more frequently in the former, exhibiting rigidity of the spine, radiating pains, slight kyphosis, and varying in intensity of deformity from very slight to such forms as bear the closest possible resemblance to the typical cases of spondylose rhizomélique. The recognition of these cases is dependent very largely upon the roentgen-ray findings, and here the irregularity in contour of the vertebræ, the evidences of osteophytic growths, the slight lipping of the vertebræ, lead to the correct diagnosis. There is no doubt that in these forms as well as in the specific there is considerable exudate, considerable thickening of the periosteum and of the meninges, all of which is not revealed on the roentgen-ray plate. And, on the other hand, it is also fair to assume that this same diagnosis may be found in persons who present no tangible bone or nerve symptoms I suspect that in many cases the symptoms are due to the exudate and to the thickened meninges rather than to the altered condition of the vertebræ themselves that are shown more or less distinctly on the roentgen-ray plate. The same roentgen-ray findings also occur in the senile period, at least as frequently in women as in men, and are often associated with other arthritic changes that are common in this period of life. We have found these senile forms of spondylitis in a number of elderly persons who have either presented symptoms of sciatica, changes in the sacro-iliac juncture, or symptoms pointing to a lumbar arthritis. The occurrence of spondylitis deformans in association with a general arthritis deformans goes without saying.

Considering the etiological factor in all of these forms of spondylitis, barring the specific, it is reasonable to suppose, as some of the French and German writers have maintained, that many of them are expressions of some chronic infection[4]. Some such have been reported as occurring after streptococcic pleuritis and after scarlet fever, diphtheria, measles, and whooping cough. That some of them may be of gonorrheic origin must also be admitted.

I am willing to join those who believe that very few of these cases will prove to be allied to the purely rheumatic disorders and yet cases do occur in which an ordinary spondylitis appears in association with general articular rheumatism. For that reason, if for no other, it will not do to discard wholly the group of rheumatoid spondylitis.

The difficulty that arises in the differential diagnosis is concerned chiefly with the question of deciding whether or not, in a given case, we are confronted with spondylitis or with spinal neoplasm. In primary neoplasm of the cord there would be very little difficulty. The roentgen plates often do not offer the expected help. In many instances we have observed spondylitic processes in the vicinity of spinal neoplasm. The entire and more rapid march of the symptoms will, as a rule, point the way to the correct diagnosis. But particularly in the cases of secondary carcinomatous and sarcomatous deposits a mistaken diagnosis can be made readily enough, although even in these forms the more rapid progress of the symptoms and the early involvement of the spinal cord and relatively slight involvement of the vertebræ will turn the scales in favor of neoplasm rather than of spondylitis.

So far as the treatment of these cases is concerned the specific cases should be treated most vigorously by intravenous injections of salvarsan, combined with intramuscular injections of mercury or by inunctions. The non-specific cases must be treated either by simple rest, by intense heat, or by such measures as it is entirely within the province of the orthopedic surgeon to suggest.

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[4] Dr. Nathan's views on the infectious origin of chronic spondylitis as reported at this same meeting are of great value.

THE NEUROLOGICAL CONDITION ASSOCIATED WITH POLYARTHRITIS AND SPONDYLITIS.[1]

By Philip William Nathan, M.D.,
NEW YORK CITY.

(A Clinical and Experimental Study from the Montefiore Home and Hospital, and the Carnegie Laboratory, Pathological Department.)

That symptoms referable to the nervous system are not infrequently associated with both acute and chronic joint disease has been recognized by all those who have studied these conditions. Even the earliest writers comment upon this association and speculate upon the interrelation of these conditions. However, even with the improved methods of clinical investigations and the more intensive studies of modern times, the nerve conditions associated with acute and chronic arthritis have not been definitely determined, and the relation between nerve and articular conditions still remains unexplained.

This is true not only of the acute and chronic polyarticular conditions which do not seriously involve the spine, but in spite of the impetus given to the study of the arthritides of the spine, by the researches of Bechterew, Strümpel, and P. Marie, it also remains true of the neural phenomena of vertebral arthritis.

Nearly all the writers upon these conditions content themselves with the mere statement that certain symptoms referable to the nervous system occur in cases of mono- and polyarthritis; and those who comment upon the causal relationship between these conditions at all seem content to follow Charcot in his view that the neural symptoms are due to the reflex influence of the arthropathy.

This, in spite of the fact that there are numerous cases on record which show definitely that the neural symptoms cannot, for obvious reasons, be due either directly or indirectly to the arthritis itself. So, for instance, there are not a few reports of amyotrophic lesions associated with, but in no way corresponding to, the distribution of arthritis following gonorrhea; and there is not an insignificant literature upon the same neural lesions which have followed infections in which the joint lesions have been evanescent or absent entirely.

My own experience has led me to believe that, aside from the atrophy and hypertonia which can, with more or less propriety, be attributed to reflex action, neurological symptoms are frequent accompaniments of polyarthritic conditions; that these symptoms are definite, and that they bear a definite relation to the underlying morbid process.

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[1] Read before the New York Neurological Society, December 7, 1915.

These neurological phenomena, which for the most part consist of muscular atrophy with spasticity, vasomotor irritation, and disturbed sensation, may be associated with either acute or chronic polyarthritis.

During the acute stages when the joint symptoms and the general reaction is marked the neural symptoms are rarely looked for, and for this reason not often described. Since I have made a practice of making a neurological examination of all patients with polyarthritis, I have found transient, and more or less permanent, spastic atrophic phenomena, evidently not of reflex origin, in a considerable number of cases of acute polyarthritis. The symptoms are not present in all, and in a considerable number of cases they are mild and continue only for a short time; in a certain percentage of the cases, however, they are pronounced and definite. The following abstract of the history of a case of acute goneitis seen in a ward of one of our best city hospitals illustrates both the tendency to overlook these symptoms entirely and the usual symptom-complex during the early stages.

A. B. became suddenly ill with intense pain running down the left lower extremity from the pelvis to the foot; the following day the left knee became swollen and extremely sensitive; he had high temperature and marked general indisposition. He was brought to the hospital, where he was given the usual antirheumatic treatment. The pain and the swelling of the knee gradually subsided, but did not wholly disappear. When I saw him, three weeks after admittance, he complained of pain in the knee and weakness in attempting to walk. The patella and Achilles reflexes were markedly exaggerated, and he had an inexhaustible ankle-clonus on both sides. The condition gradually improved.

I have found similar spastic paretic conditions, involving either the upper or lower extremities, associated with joint infections as sequelæ of gonorrhea, pneumonia, sepsis, and typhoid fever. In some instances the neuromuscular phenomena were the only neurological symptoms; more often there were also symptoms referable to irritation of the sensory nerves (hyperesthesia, radicular and lancinating pains), and occasionally vasomotor and so-called trophic skin disturbances (localized hyperidrosis, glossy skin, and edema) were also present.

The phenomena of vasomotor irritation are not likely to occur during the early stages of the chronic, and, with the exception of the hyperidrosis, are rare in the acute self-limiting conditions.

In a very considerable number of the acute infections the phenomena of neural irritation ultimately subside irrespective of the outcome of the joint disease. In some cases, however, the neurological condition persists much longer than the joint abnormality, and, in certain cases, muscular atrophy and spasticity remain as the only permanent change.

A fairly large number of the cases of chronic deforming arthritis are accompanied by musuclar atrophy and a varying degree of spasticity. The location, the duration, and the intensity of these neurological symptoms are extremely variable; and though in some instances their intensity and distribution correspond to the joint involvement, in a large proportion of the cases the two morbid phenomena are independent of each other. Thus, in some cases the joints of the upper extremity only are involved, but the atrophy and spasticity are present in the lower extremities as well; and not infrequently the abdominal and facial muscles are also involved.

In many of the cases muscular atrophy and spasticity is the earliest symptom. It not only precedes the joint involvement by a considerable interval, but it may remain the most prominent symptom throughout the course of the disease. And I not infrequently see patients with marked disability, supposedly due to polyarthritis, in whom the joint disease is insignificant, the disability being entirely due to muscular atrophy, spasticity, and permanent muscular shortening. This is unusually well illustrated in the following case:

M. M., male, aged twenty-eight years. Admitted to Montefiore Home, March 6, 1914. The disease began with pain in the right thenar eminence three years ago. Pain gradually extended first up the right arm, and within three or four days all four extremities were involved. The hands, knees, and feet were swollen. Pain and swelling subsided after a few weeks. He then noticed that his extremities were stiff and weak and he was unable to walk. He complains that he has grown weaker and more stiff during the past three years, though he has no pain when he is quiet or when the passive motion in the joints is not forced.

Chief Complaints. Stiffness and weakness of extremities. Inability to walk.

Physical Examination. Heart, lungs, and abdominal organs show no abnormalities. Blood-pressure, 122; Wassermann, negative. Contraction palmar facia of right hand; marked atrophy of thenar hypothenar eminences and the interossei of both hands. Both elbows are flexed to right angle by muscular shortening or contracture; the motion is not limited by actual joint changes, and is not painful unless forced beyond the limits maintained by muscle shortening. In the shoulders there is limitation of abduction only, the other motions, particularly rotation, being free. Both hips are flexed to almost a right angle, extension being limited by shortening of the flexor muscles. Abduction is also limited by adductor contraction; all other motions are free, and there are no evidences of active disease in the hips. Both knees flexed, the hamstrings are contracted, and motion is further limited by change in the joint structures. The feet show no signs of joint disease. Motion in the spine is partially limited. There is marked muscular atrophy and marked exaggeration of the reflexes in all four extremities and ankle-clonus on the left side. He is unable to walk because of the weakness and spasticity. The very insignificant changes in the knee are the only evidence of permanent arthritic condition.

Such a marked degree of spastic paresis without other lesions is, of course, unusual. But spastic paretic phenomena are not uncommon accompaniments of all forms of chronic deforming arthritis. It is true they are not present in all cases, and when present they are usually mild in character; they may, however, be, as in the case just cited, so marked that they completely overshadow the joint condition. Occasionally, indeed, as in the following case, the segmental nature of the lesion is even more strongly suggested by the clinical phenomena:

B. C., male, aged forty years. Admitted to Montefiore Home December 19, 1913. One year ago he began to have pains in the fingers of the right hand, but continued to work. Soon afterward he noticed a swelling of the joints between the proximal and middle phalanges of the index, middle, and ring fingers. The pain and swelling increased in severity and soon extended to his right elbow joint and then to his right shoulder. The above joints also became somewhat swollen. Following this his neck became somewhat rigid, and he began to have severe pains in his left chest. He was sent to Gouvenor Hospital, where he remained for six months. Under treatment there was considerable improvement, and he was able to go back to work again.

He worked for about two weeks, when his knees became very painful and swollen, so that he could not walk. Soon after his hips, ankles, and the fingers of the right hand became involved.

Status taken by Dr. Elliot: No cardiac, renal, or pulmonary symptoms.

Right hand: Linear globular swelling of the proximal midphalangeal joints. Carpophalangeal and phalangeal joints of the thumb enlarged and sensitive to pressure. Distal phalangeal joint is enlarged. Motion is restricted.

Right elbow can be flexed to an angle of 45 degrees and can be extended to 135 degrees. Supination and pronation restricted.

Motion in right shoulder somewhat restricted, but all movements are present.

The conditions in the left hand and fingers are the same as in the right. There is more fulness of the metacarpophalangeal joints of the index finger. Flexion and extension is apparently normal. Supination and pronation restricted on account of pack in carporadial joint. Motion in the left elbow and shoulder practically normal.

Motion in both ankles is painful. Passive motion is normal. Both knees are painful to pressure; contour is obliterated by swelling and doughy in character. The patellæ are mobile.

There is thickening of the periosteum of both ilia, and they are very sensitive to pressure.

Urine: Negative for albumin, sugar, indican. Microscopic examination negative.

Blood-pressure, 120.

Wassermann: Negative.

Blood: Hemoglobin, 85. Red blood cells, 4,400,000. White blood cells, 10,200; neutrophiles, 60; eosinophiles, 2; small lymphocytes, 20; large lymphocytes, 14; large mononuclear leukocytes, 2; basolymphocytes, 1; myelocytes, 1.

Status when he came on my service (January, 1915) was as follows:

General condition poor. He walks with marked spastic gait and can only get around with considerable difficulty. He has no pain when quiet, but has considerable pain on flexion and extension of the knee. He can voluntarily extend the knee after some effort, when it becomes stiff in the extended position. After much effort he can gradually flex the knee after it has been extended, when the knee becomes stiff in the flexed position; that is, he has alternate flexor and extensor spasm of the muscles of the knee.

A similar condition exists in the right hand. As a rule, he has spasm of the extensions of the fingers. When, however, the flexors are irritated (struck with a percussion hammer a few times) the spasm leaves the extensors and affects the flexor muscles. The left hand is free. The right abdominal reflex is much more marked than the left. There is marked muscular atrophy of the muscles of the right hand, arm, and both lower extremities.

The spine is somewhat stiff, but not completely immobilized. There is pain on percussing the spines in the upper dorsal and dorsolumbar regions. There are no signs of active joint disease anywhere.

Such motor phenomena as I have here illustrated may or may not be accompanied by sensory and vasomotor disturbances. Radicular and lancinating pains are very often present in acute polyarthritis and during the early stages of chronic deforming arthritis. Paresthesia, particularly akroparesthesia, are very common; and transient and long-continued hyperesthesias are present in a very large proportion of the cases. Definite segmental areas of anesthesia are here, as in analogous conditions, difficult to demonstrate.

Vasomotor symptoms and the so-called trophic skin lesions are not as common as the other neurological symptoms. When they are present there is always some neuromuscular abnormality, though such symptoms may exist without signs of sensory involvement. The gravest cases of so-called rheumatoid arthritis are those in which severe generalized joint involvement is associated with spastic paretic and vasomotor changes. In these cases the muscular atrophy is often extreme, the skin is thin and markedly edematous or glossy, and the blood-pressure remarkably reduced. Decubitus ulcerations of the skin, degeneration of the nails, etc., make the condition of the patients pitiable. Fig. 1 shows the extreme atrophy and trophic skin disturbance in such a case. Fig. 2 shows another case of chronic deforming arthritis with amyotrophy and (so-called) neurotic edema.

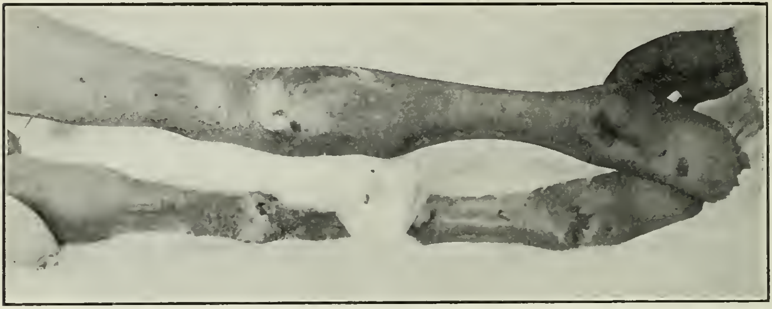

Fig. 1.—Extreme muscular atrophy, pigmentation and ulceration of the skin in deforming arthritis with radicular involvement.

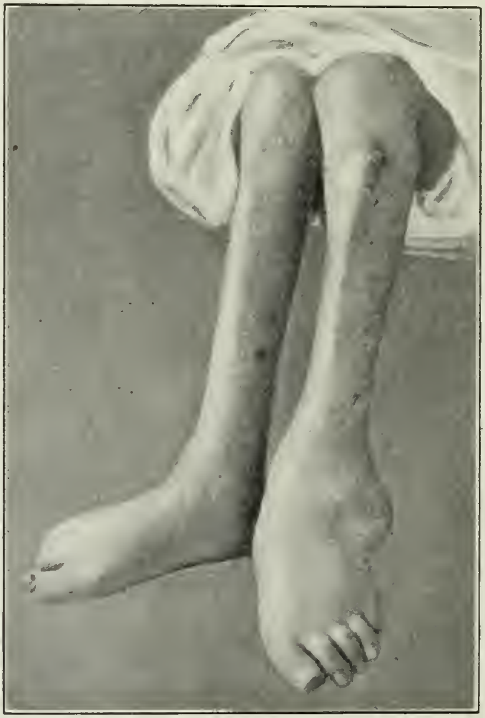

Fig. 2.—Neurotrophic edema, ulceration, and pigmentation of the skin in a case of deforming polyarthritis with radicular involvement.

Various combinations and all degrees of these evidently organic neurological phenomena are to be found in the various forms of polyarthritis. They occur in cases with and without evident vertebral involvement; they may be severe in cases of mild joint disease; they may be mild or absent in long-continued and severe forms of generalized arthritis; they may be transient or permanent; and they may or may not be combined with signs of organic disease (heart, kidneys, etc.) elsewhere. Moreover, though the condition may soon become stationary or completely disappear, after the signs of general illness have subsided and the joint symptoms are no longer progressive there are cases in which the neurological condition progresses just as it does in amyotrophic spinal conditions, invading segments from above downward, or *vice versa,* with or without definite regularity.

To judge from the variability of the neurological symptoms the deleterious influence which attacks the spinal nervous system in these cases must vary considerably in intensity, the region or regions it attacks, and the manner in which it produces the pathological changes. However, notwithstanding the extreme variability in location and intensity, the fundamental constituents of the neurological symptom-complex are practically always the same, namely, a hypertonic paretic condition with or without disturbed sensation, and vasomotor and trophic skin abnormalities.

Only in rare instances does one find definite areas of anesthesia associated with a hypertonic condition, and equally infrequent are flaccid paralyses of individual muscles, with or without hypertonic conditions elsewhere.[2]

If now we turn to the symptoms which are present in the evidently vertebral arthritides we find the same variability as to the intensity and to the location of these conditions, and the same absence of a definite relation between the intensity and in many cases even in the location of the neural and articular lesions. Since Bechterew, Strümpel, and P. Marie have published their findings the literature on this subject has grown steadily more unwieldy; many classifications of the vertebral condition both as it relates to character of vertebral involvement, to the joint involvement elsewhere, and as it relates to the neurological status, have been proposed, but so far no one has been able to show that there is a definite relation between these conditions.

The symptoms described by Bechterew are fundamentally the same as those we have just shown to be associated with arthritic conditions generally, namely, spastic atrophic, hypertonic, and irritative sensory phenomena, with occasional anesthesia and flaccid paresis.

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[2] In a case recently admitted to the Montefiore Home there was a paretic condition of the left gastrocnemius muscles, absent Achilles reflex, associated with polyarthritic and spastic paretic changes elsewhere.

From my own material, which is considerable, and from the case reports I have been able to find in the literature, the neurological condition apparently bears absolutely no definite relation to the character of the joint lesions. Definite nerve symptoms may be present in cases with marked spinal stiffness, with kyphosis, lordosis, or lateral deviations of the spine; they may be totally absent in cases presenting exactly similar ankylotic and deforming conditions. Cases with practically very little deformity without any ankylosing condition may, on the other hand, present marked motor and sensory abnormalities, while others with complete bony ankylosis of the bodies of the vertebræ and even the costovertebral joints may show no neurological change whatsoever. Fig. 3 is a picture of a negro with complete vertebral ankylosis and marked kyphosis without neural involvement. This boy continues his occupation as newsboy without apparent discomfort.

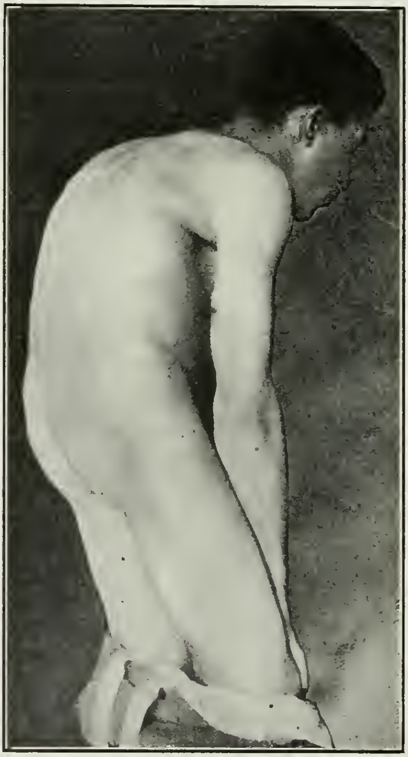

FIG. 3.—Infectious arthritis of the spine with complete ankylosis. There is no radicular involvement and, except for the deformity and stiffness of the spine, this man is perfectly well.

Nor does the fact that the hips or the shoulders are involved seem to bear any relation to the presence or absence of the neurological symptoms. These symptoms are just as often conspicuous in the types of Strümpel and Marie as they are in the one described by Bechterew,[3] and equally as often totally absent in the final stages of the conditions.

As far as the spondylitis is concerned this variability of the symptoms may be partly explained on the ground that the neural phenomena may be present during the early stages of the disease and disappear at some later time; or, on the contrary, the neurological changes may come on insidiously, when they will, of course, be absent during the early stages. Thus it will depend upon the period when the patient comes under observation whether these symptoms are definitely present or absent. But this only partly explains the condition of affairs, for it does not account for the variability of the symptoms themselves nor for the fact that in some cases the symptoms are absent throughout the course of the morbid process.

I have for sometime thought that all the peculiarities here enumerated could be readily explained upon purely anatomical and mechanical grounds, but the difficulty in procuring autopsies in such cases has made the actual demonstration of the lesions in the human subject impossible.

It must be evident to everyone who has had neurological experience that the neural symptoms here described must be due to nerve-root irritation or compression, and in the very severe cases, perhaps actual spinal-cord compression. Curiously enough, few of the writers upon this subject have thus interpreted these symptoms; nor, except in a few instances, are the conditions in the epidural space, the intravertebral foramina, and the costovertebral joints considered in the autopsy reports to be found in the literature. It is not surprising, therefore, that actual neurological findings have been for the most part negative, and the actual causal relation between the joint and neurological conditions has remained unexplained.

When, therefore, I found that I could induce chronic non-suppurative polyarthritis in animals, I immediately determined to examine the conditions in the vertebræ and the spinal canal in order, if possible, to demonstrate morbid changes in these structures. The results of these investigations are here presented.

It has been shown by J. Koch that the bone marrow, like the liver and spleen, is influential in filtering microörganisms from the blood. Microörganisms can nearly always be recovered from the bone marrow in the spongy portions of the bones, when they have been injected into the blood stream of animals, and they are practically always found in these situations in the human subject dead of an infectious disease.

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[3] Unless one chooses to classify only those cases of spondylitis with neural symptoms as belonging to the Bechterew type.

J. Koch was enabled to produce polyarticular conditions in the dog (much resembling acute arthritis in man) by injecting streptococci. In a number of his animals he secured polyarticular conditions which markedly resembled the acute polyarthritis usually designated as acute articular rheumatism.

The results of my own experiments confirm the findings of Koch in every particular. I have found that following the injections of hemolytic streptococci I could produce various forms of bone and joint lesions. These lesions were in some cases acute, in others they were subacute or chronic. Actual suppuration never supervened. Of eighteen dogs which received the streptococci directly into the femoral vein, six showed both clinical and postmortem bone and joint abnormalities in the spinal column.

After a stage of incubation which lasted about three days, all the animals had a rise in temperature and signs of general indisposition. Following the initial rise in temperature, the six animals which showed the vertebral changes postmortem seemed to be disinclined to walk and also seemed weak on the legs. The joints, however, though swollen, were not apparently painful, and the disability was evidently due to weakness. In one of the dogs (dog 2 of my series 1) the joints were apparently unaffected. But this particular animal, like the others which had spinal involvement, remained weak even after the temperature had subsided (a few days after the onset of the symptoms), and died twenty-eight days after the injection of the bacteria.

With the exception of the last mentioned the animals with spinal involvement were killed on the eighth, sixteenth, twenty-first, forty-eighth, and ninetieth day after injection, respectively.[4]

The conditions of the bones and joints generally will be fully described in another paper. What is of interest here as bearing upon the spinal condition is the fact that during the earlier stages of the disease, besides the changes in the epiphyseal marrow, the infection involves the subperiosteal region of the epiphysis. The inflammatory condition spreads from this situation to the region of the capsular insertion and thence directly invades the capsule itself and the joint interior.

Joint swelling, when present, is due not alone to increase of the joint fluid, but during the earlier stages it is due to peri- and para-articular exudate as well. This peri- and para-articular exudate was present in all the animals which showed joint involvement at all, when the animals were killed during the early stages of the disease. The exudate was not bacteriologically examined in my cases, but Koch found it sterile in all his cases, even when the streptococci could be demonstrated in the epiphysis.

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[4] The protocols are omitted to save space. They tally, with the exceptions mentioned, with those of Koch.

As has been said, in six of my cases there were changes in the spine. On opening the spinal canal one immediately became aware of an epidural exudate. The epidural areolar tissue was markedly edematous, of a gelatinous consistency, and in some places completely filling the epidural space with a semisolid opaque mass. The location and extent of the edema was irregular. In one case it extended continuously from the middorsal to the lumbar region.

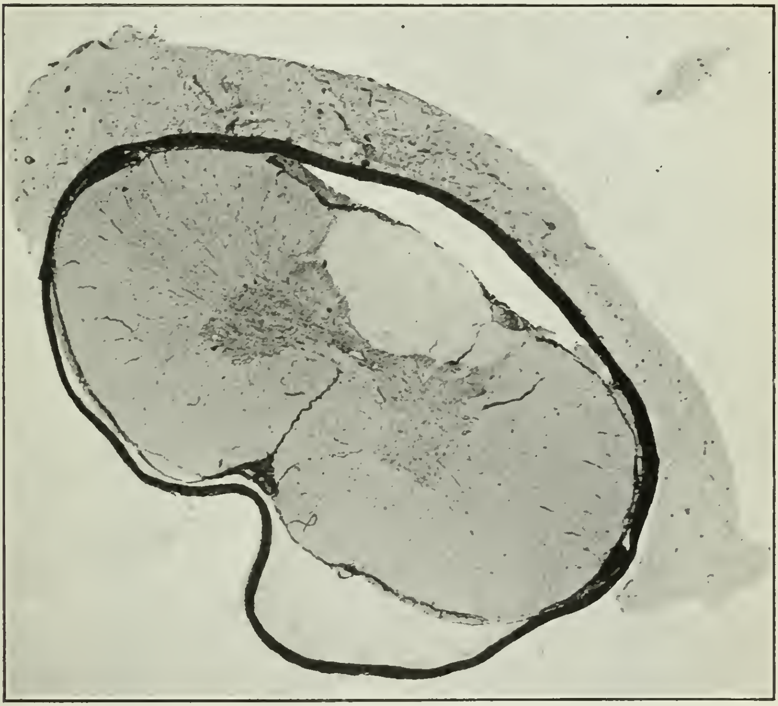

FIG. 4.—Section of spinal cord showing beginning of organization of the exudate on the dura.

In the others the exudate was discontinuous and involved one or more areas, varying in extent and location. Except where the edematous and thickened areolar tissue was closely adherent to the dura the dura and the spinal cord showed no changes microscopically. The vertebral veins were markedly dilated and congested (Figs. 3 and 4).

A number of the costovertebral joints were involved in all the cases. These presented both an intra- and peri- and para-articular exudate in the earlier stages. Later there was considerable thickening of the connective tissue in their neighborhood, and there was distinct beading at the epiphyseal junction of the rib.

The periosteum of the vertebral bodies was distinctly thickened in a number of situations. Both the lower and the upper (*i. e.*, the celomic and the side facing the spinal canal) were so changed, but the location and extent of the thickening was extremely irregular. In some cases (dog 3 which died on the twenty-eighth day) the bodies of nearly all the thoracic vertebræ were involved, and the surface of the vertebræ on both sides present a somewhat nodular appearance macroscopically. In dog 1, killed on the eighth day, the thickening of the periosteum could not be seen macroscopically. In dog 6 only three vertebræ seemed to be affected.

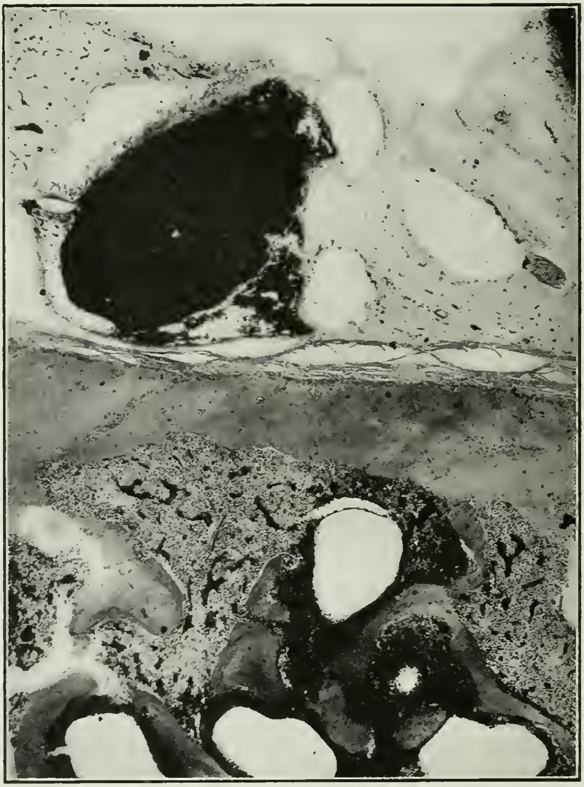

Fig. 5.—Epidural surface of body of the vertebra. Exudate under the periosteum and in the epidural space. Dilated vein containing thrombus. The hyperemia and medullary cell proliferation is also shown.

The affected vertebræ were distinctly softer than the normal in all the cases and could be sawed through with considerably less difficulty than those of the normal dog. There were no signs of actual deformation in any of the cases, and in only one dog (No. 6) was there any evidence of involvement of the vertebral synchondroses with rather insignificant limitation in the movements of the spine.

Microscopically the structure of the vertebral bodies showed changes corresponding to those found in the epiphyseal ends of the long bones. There was marked increase in the blood supply and gradually increasing hyperplasia of the marrow cells. The marrow cells increased in numbers until they completely filled the marrow spaces, and continuing to proliferate the cells encroached upon and gradually displaced the bone trabeculæ. Then more and more bone becomes absorbed, neighboring marrow spaces become confluent, and the bodies of the vertebræ become rarefied. In some situations the rarefication is extreme (for instance in dog 5, forty-eight days), the bone trabeculæ are very few in number, very thin, and the body of the vertebræ almost completely made up of lymphoid marrow.

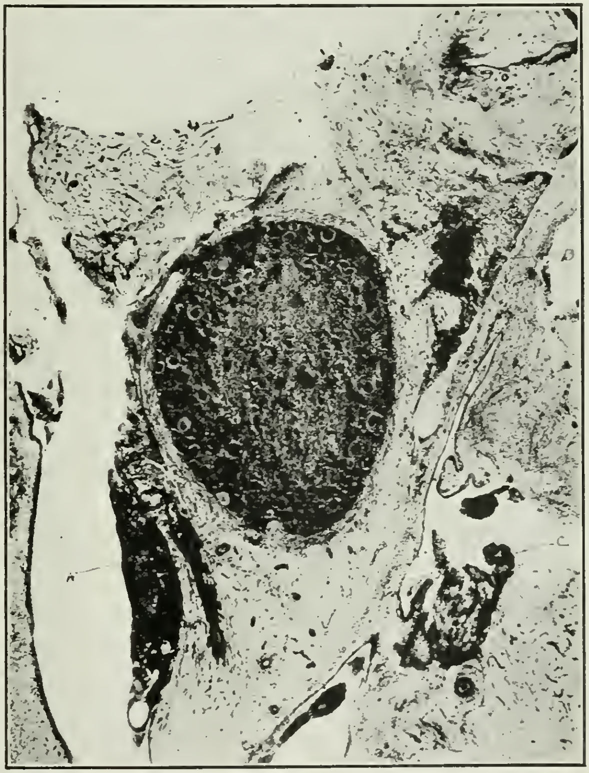

FIG. 6.—Exudate surrounding spinal ganglion. (*a*) Vein containing thrombus. (*b-c*) Extravasated blood.

The details and the termination of the marrow changes cannot be described at the present time. They are, as has been said, similar to those found in the epiphysis of the long bones, and will be more fully considered in another paper. One fact, however, must be emphasized, namely, the changes in the bone may subside and the bone trabeculæ are then more or less completely restored.

What interests us particularly at the present time are the subperiosteal and juxtaperiosteal changes. These changes affect both the celomic and the epidural sides of the bodies of the vertebræ, and in both the conditions are similar. More important, because of their bearing upon the neural involvement, are the morbid conditions as they affect the epidural periosteum. Here, as elsewhere, the disease is at first focal. The focus may spread rapidly, or a number of foci become confluent, and there is a considerable hyperemic area. Following the hyperemic stage the subperiosteum becomes edematous and as the pathological process advances the adjacent structures become edematous as well. In some cases the edema subsides, leaving the adjacent tissue spaces dilated, or the edematous condition is followed by connective-tissue proliferation, when the nodular condition of the periosteum, referred to above, ensues.

I have not been able to demonstrate the streptococci in the lesions here described, but these lesions correspond exactly in their essential features with those which occur elsewhere, and in which J. Koch has demonstrated the presence of the injected organisms.

Coincident with the subperiosteal changes the tissues in the neighborhood become congested and edematous. The periosteum is raised from the underlying bone and the edema spreads to the neighboring areolar tissue in the epidural space, intravertebral notches, etc. It is to be noted that these changes, particularly the exudate, correspond exactly to the peri- and para-articular exudate of the joints of the extremities, and for this reason the exudate is in all probability sterile. This is an important consideration, for it accounts for the fact that the actual inflammation, as far as the findings in the present series are concerned, did not extend to the dura.

In some, but not in all the cases, the epidural exudate became organized. My work in this respect is not complete, but so far as I can make out at the present time it appears that the epidural exudate may be completely absorbed, or it may become generally or locally and to all appearances permanently organized. At any rate I have found definite signs of organization and localized areas of connective-tissue proliferation in several of my cases.

The condition in or near the costovertebral joints, and in the neighborhood of the intervertebral notches, differs in no way from those just described. In the epiphyseal ends of the ribs the tendency to connective-tissue proliferation and permanent periosteal thickening is much more conspicuous and leads to the condition referred to as beading of the ribs, and to coarctation of the intervertebral foramina.

It is impossible, without greatly exceeding the time at my disposal, to describe the microscopic findings in detail. It is evident that the morbid conditions in the spine and the adjacent tissue in streptococcus infection in the dog are fundamentally the same as those found in other parts of the skeleton. There are both endosteal and subperiosteal processes which are manifest, clinically and pathologically, by intra-, peri-, and para-articular joint exudations in the early stages, and which are followed by transient relaxation or more or less permanent connective-tissue hyperplasia. In the diarthrodial joints I have been able to follow the process still further. For the present purpose, however, the demonstration of the changes to the point of connective-tissue hyperplasia is sufficient.

The mere fact that there may result an epidural exudate as a result of streptococcus infection is illuminating. That similar conditions may be and are very likely present in the human subject is borne out not only by the fact that we can demonstrate symptoms which strongly suggest that such a condition may exist, in many cases of polyarthritis in man, but the analogy is still more strongly suggested by the fact that the marrow changes and microörganisms have been demonstrated in the human subjects. Fraenkel was able to demonstrate the presence of the typhoid bacillus and the pneumococcus in the marrow of the bodies of the vertebræ in a number of cases dead of these diseases. And although he does not describe the periosteal and the epidural conditions which I have found present in the dog, his description of the marrow changes are certainly analogous. Moreover, Bechterew in his report of the autopsy of one of his cases describes changes in the epidural space involving the nerve roots, which are certainly analogous to those I have here described.

That the streptococcus, pneumococcus, gonococcus, and no doubt other microörganisms may cause analogous conditions in the joints and peri- and para-articular structures is well known. The clinical manifestations of such a morbid condition are common in cases of general infections due to a variety of microörganisms, conspicuously so with the gonococcus infection.

As analogous conditions exist in the other joints and similar marrow changes and microörganisms have been demonstrated in the bodies of the vertebræ in the human subject, it seems to me only fair to assume that similar or analogous epidural conditions must be held accountable for the neural symptoms in the human subject.

That such conditions completely account for the neural symptoms is evident. The symptoms present in all forms of arthritis, whether acute or chronic, early or late, are those of radicular or spinal irritation or compression. These symptoms, transient or permanent, mild or severe, complete or incomplete, can only be caused by changes not in the roots themselves but to altered mechanical conditions in the epidural space or the intervertebral notches.

When there is extensive inflammation and exudation the symptoms will be severe and extensive in distribution; when the condition comes on acutely and subsides we may have, as we often do, severe but transient neurotrophic conditions. In some cases the clinical manifestations are those of a localized process, in others the symptoms are those of a chronic, transient, or a permanent change in the juxtaradicular region.

In the dog the pathological changes correspond exactly to such clinical phenomena. There are cases in which the exudate and the inflammatory changes are more or less localized, those in which it pursues its course insidiously (dog 6, which never showed marked indisposition, but gradually became slightly lame, and when killed on the ninetieth day was found to have only two localized nodes of connective tissue near the intervertebral notches of the fifth and seventh thoracic vertebræ) and those in which the morbid process had apparently led to permanent changes.

It is evident, too, that the infectious process in the dog may lead to definite interference with the functions of the spinal roots without actually interferring with the gross mobility of the spine, which again readily suggests why in some cases we have pronounced symptoms of root involvement in the human subject, though the spine is only partly or not at all immobile.

On the other hand, the fact that the spine may be more or less completely immobile and even markedly deformed, without recognizable symptoms of neural involvement, does not, at first sight, appear so easily explained. When, however, it is considered that the disease may involve the thoracic or abdominal side of the bodies of the vertebræ and the intervertebral syndroses, or the small joints of the spine, and there cause the permanent changes which lead to ankylosis; and that in this case the epidural changes, if they have existed, were transient, the reason why neural symptoms may be absent in such cases becomes apparent. On the other hand, it goes without saying that epidural conditions, and as a consequence clinical manifestations of radicular or even spinal compression, may be, as they are in tuberculous spondylitis, coexistent in such cases.

If then my assumption that the pathological conditions are analogous to those we find in the experimental conditions in the dog is correct, neural symptoms associated with polyarthritis and spondylitis are caused not by the actual involvement of the nervous system in the pathological process, whatever its nature, but by mechanical conditions which supervene either during the activity of or after the actual pathological condition has subsided.

No one who has had much to do with conditions which are apt to cause root irritation or compression—spondylitis, spinal tumors, fractures, and distortions of the spine, etc.—can doubt that the symptoms met with in the human subject are those of mechanical interference with the functions of the nerve roots. That such neural symptoms follow or accompany general infections of unknown origin, pneumococcus and gonococcus infections cannot be questioned. The literature contains numerous examples of such conditions. In all these cases, and in a considerable number which I have seen myself, the joint findings clinically and postmortem are all analogous to those in the dog; and though, except in a few instances, the actual spinal conditions have not as yet been demonstrated, I think it fair to assume that, inasmuch as the joint conditions are more or less perfectly analogous, the spinal conditions must be analogous as well.

Hence, as the neural symptoms in man are those of mechanical root compression and irritation, and as the pathological change following experimental streptococcus infection in the dog correspond exactly to one which would cause such a mechanical compression and such symptoms in man, I think the evidence that the pathological conditions in man and the dog are analogous is fairly conclusive.

I do not, however, mean to imply that all cases of spondylitis or polyarthritis which are associated with neural symptoms are streptococcus infections. All the microörganisms which cause non-suppurative inflammation in man induce analogous changes in the bones, the joints, and the peri- and para-articular structures, and, as a consequence, may induce similar pathological and mechanical conditions in or near the spine. That a hemolytic streptococcus can cause spinal lesions with or without neural lesions is certain, for we have had such cases in which the microörganism was isolated from the blood under observation.

Whether all conditions associated with neural changes are infective is another question, and one more difficult, at the present time, to answer without at least some hesitation. In the cases with definite acute onset, temperature and general constitutional reaction, etc., it may, in the light of our present knowledge, be assumed that the cause is an infection. In the cases seen after the initial symptoms have subsided, however, the history given by the patient, which, as I have found to my cost, is nearly always unreliable, might lead one to believe that the disease is one with an insidious and progressive course, without definite onset or general reaction—one, in fact, due to some constitutional anomaly. When, however, the patient's subjective impressions are disregarded, the facts do not lend themselves to this interpretation. In the first place the actual changes, clinical and anatomical, in the joints are those of an inflammatory condition which, in a large proportion of the cases, no matter how chronic the course is self-limited. Moreover, the objective symptoms exactly correspond to those in cases of undoubted infection. Furthermore, it must be remembered that the stage of general infection in these cases may be extremely short, and the general reaction not only mild but evanescent.

It has been shown by a number of experimenters that the microorganisms injected, disappear from the blood in a remarkably short time. In Koch's and in my own experiments after a very short period of illness practically all the animals showed no general symptoms, although the pathological condition in the skeleton, etc., continued to progress. Hence, the presumption is that, in animals at any rate, the skeletal lesions are local in these cases, causing no general symptoms after the microörganisms have disappeared the blood and the toxemia caused by the initial invasion has subsided.

It is not unreasonable to assume that similar or analogous conditions occur in the human subject. In a large number of undoubted infections the initial disturbance is mild and of short duration, and may escape an unobserving patient entirely. As a matter of fact, I have known patients to have temperature as high as 103° without feeling at all feverish or ill. Under such circumstances it is not at all unlikely that in many cases the initial disturbance is so mild and evanescent, or the patient so unobserving, that these symptoms are overlooked, and thus the condition may be mistaken for a chronic constitutional malady.

Conclusions. Clinically, the neural symptoms associated with polyarthritis and spondylitis are those of moderate radicular or spinal irritation or compression. The variation in the symptoms can be fully accounted for by variations in the onset, the location, the intensity, and the course pursued by the pathological process causing the periradicular changes. Experimentally it has been shown that the vertebral changes which are induced by inoculating dogs with streptococcus are similar to those in the skeleton elsewhere. These changes are endosteal and subperiosteal inflammation, concomittant with a sterile intra-, peri-, and para-articular exudation. In the spine this exudate involved the epidural space and the vertebral notches; it was of such a nature that it must perforce have caused root or spinal irritation or compression. In some cases the findings lead me to conclude that the exudate is finally absorbed; in others, however, there could be no doubt that the exudate was followed by permanent connective-tissue changes.

These changes exactly correspond to a condition which in the human subject would lead to the neurological symptoms we have shown to exist in cases of polyarthritis and spondylitis.

As the spinal lesions in the dog are exactly the same as the peripheral joint lesions, and as peripheral joint lesions in the dog and man are absolutely analogous; and as we have no reason to believe that the bones and periarticular structures of the spine in man react differently to deleterious influences than those of the skeleton generally, we must assume that the vertebral and epispinal morbid conditions in man are also analogous to those we have been able to demonstrate in the dog.

Hence, when the neurological symptoms here described are associated with arthritis it must be concluded that the spinal column is involved in the morbid process, and that the vertebral changes consisting of endosteal and subperiosteal inflammation have lead to epidural and perispinal exudation, causing root or slight spinal compression, which may or may not be permanent.

It therefore follows that the neural symptoms we have described as existing in the arthritis conditions are due to epidural or periepidural exudations, and the differences in the distribution, intensity, and permanence depend upon the distribution, the intensity, and the sequelæ of the epidural and perispinal process.

All these conditions are in all probability due to infection. The infection is not due to a specific microörganism, but may be caused by any organism which will produce non-suppurative inflammation in the bones and joints. The presence of nerve symptoms in some cases of polyarthritis or spondylitis, and their absence in others, must be ascribed to differences in the location and not to differences in the morbid condition which caused the spondylitis or polyarthritis. With the demonstration of these data, and assuming that my conclusions are correct, the significance of a number of perplexing symptoms occurring in the chronic deforming arthritides becomes evident. In the first place the much debated question of the neural origin of the chronic deforming arthritis is more or less definitely answered. It is certain, at any rate, that in the majority of cases the neural symptoms are due to mechanical disturbances in the spinal canal and that these mechanical disturbances are secondary to skeletal conditions. It therefore becomes unnecessary to classify the spondylitides according to presence or absence of neural symptoms, the mode of progression, or the involvement of the ribs and joints of the extremities. Whether these structures are involved or not is simply an accident of localization, and does not depend upon peculiarities or essential differences in the etiology or the pathogenesis of the morbid process.

It is then no longer necessary to specify by name the type of spondylitis, Bechterew, Strümpel, P. Maire, etc.; these conditions are not essentially different; they are all simple variations in the location of some inflammatory condition which, like all inflammatory conditions, may be acute or chronic, transient or progressive, with or without permanent damage to the tissues involved.

Moreover, if my deductions are correct, the reason why so many cases of polyarthritis present muscular atrophy and akroparesthesias in the early stages or even in the pre-articular stages becomes evident. In such cases, no doubt, the epidural surfaces of the vertebræ are involved before the peripheral articulations.

Upon these grounds, too, the origin and pathogenesis of those forms of chronic deforming arthritis in which the inflammatory joint changes are associated with gradually increasing weakness, trophic skin changes (edema, decubitus, ulceration, etc.) become clear. In such cases, so perplexing to the clinician, the joint changes point definitely to an inflammatory condition while the absence of temperature, the hyperesthesia, the spasticity, exaggerated reflexes, fibrillar contractions, increasing weakness, the neurotic edema, the hyperidrosis, the cold extremities, and the low blood-pressure lead one to suspect a neural condition combined with or secondary to an internal secretory anomaly. It is only when one has seen and closely observed such cases for years that one becomes aware of the fact that the joint and bone condition which was first inflammatory later becomes stationary and quiescent, and that the mechanically induced neural changes are in a large measure responsible for the pitiable condition of these patients. So in the case of which illustrations are here shown (Fig. 2). The patient has absolutely no signs of progressive joint disease; his extremities, though somewhat deformed, can be passively moved, and he has some active, painless motion in the upper extremities; but he is unable voluntarily to move the lower extremity at all, and must be lifted from the bed into a chair, etc. He has no pain and his symptoms in no way differ from those due to moderate mechanical radicular or spinal compression. In the beginning the symptoms were entirely articular and the disease ran the course common to all subacute and chronic arthritic inflammations. Such cases are not then, as has been supposed, primarily neural, for the articular symptoms may precede the apparently progressive neurological condition. The nerve phenomena are secondary to the skeletal conditions.

These facts are also important from a prognostic and therapeutic stand-point. It is evident that the patients with long-continued neural phenomena are not amenable to mechanical and surgical treatment, and these neural phenomena, unless they disappear early in the disease, are permanent. Hence, the prognosis in cases with well-developed and long-continued symptoms of radicular irritation or compression is unfavorable; while in the cases with marked joint involvement without nerve changes there is always a chance of improvement.

I wish to thank Dr. Noble, of the bacteriological department of the Carnegie Laboratory, for the bacteria used in my experiments. I can but inadequately express my thanks to Dr. Symmers, of the pathological department of the Carnegie Laboratory. It is entirely due to his kindness in supplying me with space and material that I was enabled to carry on this work.

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A STUDY OF THE INVOLVEMENT OF THE BONES AND JOINTS IN EARLY SYPHILIS.

By Udo J. Wile, A.B., M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, UNIVERSITY OF MICHIGAN, DEPARTMENT OF MEDICINE AND SURGERY,

AND

Francis E. Senear, B.S., M.D.,

INSTRUCTOR IN DERMATOLOGY AND SYPHILOLOGY, UNIVERSITY OF MICHIGAN, DEPARTMENT OF MEDICINE AND SURGERY, ANN ARBOR, MICHIGAN.

The conception that syphilis in the early weeks and months of the infection attacks for the most part the superficial structures, and that the severe visceropathies and syphilitic disease of the bones and joints belong rather to the group known as the late sequelæ, is without doubt due to the fact that there has been little opportunity for studying the disease in its incipiency, as is possible with other diseases. It is only within very recent time that the hospital bed has become available for the freshly infected syphilitic. With the increased facilities for study of the disease early in its course it has become more and more apparent that all of the deeper structures are affected early in the course of the disease.

During the past four years we have been enabled at our University Hospital clinic to give particular attention to such phases of early syphilis as have not been previously studied. In all of our cases we have paid particular attention to the involvement of the nervous system, general health of the individual, the question of loss of weight, the involvement of the spleen and liver, and the involvement of the bony structures. Those phases dealing with the spleen and nervous system, together with such data as bear upon them, have been made the subject of a previous communication.[1]

That the bony structures, including also the articulations, are involved as late or so-called tertiary sequelæ is of course well-known. The occurrence of various arthropathies and bone lesions form a not inconsiderable part of the pathology of these structures. The same holds true of such involvement in so-called hereditary syphilis. A surprisingly small literature, however, exists dealing with the involvement of the bones and joints as part of the early manifestations of syphilitic infection.

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[1] Wile and Elliott, A Study of Splenic Enlargement in Early Syphilis, Am. Jour. Med. Sc., 1915, cl, 512. Wile and Stokes, A Study of the Spinal Fluid, with Reference to Involvement of the Nervous System in Secondary Syphilis, Jour. Cutan. Dis., September, 1914, p. 607. Wile and Stokes, Involvement of the Nervous System during the Primary Stage of Syphilis, Jour. Am. Med. Assn., 1915, lxiv, 979. Wile and Stokes, Further Studies on the Spinal Fluid, with Reference to the Involvement of the Nervous System in Early Syphilis, Jour. Am. Med. Assn., 1915, lxiv, 1465.

We have studied during the past two years, with particular reference to early bone and joint involvement, 165 cases of syphilis in the primary and secondary periods. In all cases the long bones were carefully palpated and percussed for tenderness, and a careful note was made on the subjective symptoms pertaining to the bone and joint involvement, and all of the joints were carefully examined for objective lesions and functional impairment. In a few cases in which objective pathology was noted the roentgen-ray was also used. As in our previous communications we have attempted to show the possible relationship between the involvement of the various symptoms and later to demonstrate if there existed any predilection in the cases infected, for one or more particular systems. For this reason, in each case, parallel tables have been prepared, noting in each case the type and extent of the cutaneous lesions, the involvement of the nervous system, and the involvement of the general health. In all 60 cases of the 165 were found to have symptoms of objective findings referable to the pathology of the osseous system.

General Health. Of the 60 cases in which bone or joint involvement was found, 36 showed some definite constitutional disturbance due to their syphilis. Thus in 18 cases the general health was severely affected, as attested by severe anemia, debility, and a great loss of weight. Eight cases showed a mild involvement of the general health disturbance, the loss of weight, anemia, and debility being less marked, although the patient was definitely ill. The remaining 10 cases showed only a slight loss of weight and a mild degree of anorexia. The 24 remaining cases were entirely devoid of constitutional symptoms. Thus of the 60 cases in which the bone and joints were involved, 60 per cent. of the skeletal involvement was found associated with general health disturbance.

Type of Eruption. The analysis of the eruptive phenomena associated with bone involvement showed no apparent relation between the two to exist. All types of syphilides in about an equal proportion were found to exist with the bone manifestations.

Involvement of the Nervous System. In 31 of the 60 positive cases in our series careful neurological examination was made. Of these, 14 gave positive findings of the spinal fluid, together with associated neurological findings, while 17 were found to be uninvolved. Forty-five per cent., therefore, of the cases in which bone and joint involvement was present were cases also of neural syphilis. A previous investigation of all cases of secondary syphilis in this clinic with reference to early involvement of the central nervous system showed 70 per cent. of the cases involved. The marked difference between the figures in all cases of secondary syphilis and those which showed bone and joint involvement suggests an inverse ratio between the involvement of these two systems.

SPLEEN. In about 30 per cent. of those cases in which the bones and joints were involved, definite splenic enlargement could be demonstrated.

With regard to the development of the bone and joint manifestations, it is interesting to note that of the 60 cases, only 3 could possibly have been associated with definite traumata. In 57 the involvement seemed to be entirely spontaneous. This is in striking contrast to the development of the bone and joint manifestation in the later stages of the disease, in which the element of trauma is an all-important factor in the development of the pathology.

In considering the influence of early and efficient treatment upon the development of bone and joint syphilis it is interesting to note that in our series 41 cases had received absolutely no treatment before entering the clinic; of the remaining 19, 6 had received salvarsan and mercury combined, and only 2 had had intense mercurial treatment. Of the remainder the treatment had been desultory. In other words the vast majority had received little or indifferent treatment, and only one or two had received efficient treatment.

The symptomatology of the cases is as follows: 27 cases showed involvement of the bones only; in 21 the joints were affected independently; in the remaining 12 cases the bones and joints were involved together.

PAIN. In all but one case in which the bones were involved more or less pain was present. This varied from a dull intermittent pain described by some patients as a "dragging sensation" to the most exquisite, sharply localized tenderness. For the most part the pain was nocturnal in character and was relieved somewhat by exercise.

It required in many cases the most careful examination of the long bones to determine small foci of localized tenderness. The points of maximum tenderness were in some cases so small that unless each portion of the bone was palpated one could easily have missed them. Particularly is this true of such cases in which the pain was not spontaneous but one brought on by pressure. In not a few cases in which pain was complained of in the long bones it was impossible by methods of palpation or by the most careful examination to determine any localization of the pain. Indeed, the patients complained of bone pains without themselves being able to localize any point of tenderness. The character of such pain was rather dull, and in a few cases the patients described it as deep. We are inclined to believe that such pain was distinctly medullary, and in our experience such pain is not so readily amenable to treatment as is that of the periostitis or other more superficial points of tenderness, marked on the surface of the bone. A few patients who complained of pain in the muscles were found, on examination, actually to have points of tenderness along the periosteum or actual periosteal nodes.

Objectively, periostitis was the most frequent clinical finding. The tibia was thus involved in 8 cases examined and the sternum was next in frequency, the skull and ribs next. The clavicle was the only site in which the periosteal node was found to be absolutely painless.

JOINTS. Arthralgia was the most common finding referable to the articulations. It was present in 17 of 21 cases studied. The pain, as in the cases of the bones, was for the most part nocturnal, and was also relieved by exercise. In the order of frequency the ankles, the metatarsophalangeal joints and the elbows were affected, and in one case the elbow and shoulder-joint of the same side were affected. Pressure on such joints was always followed by sharp pain. In all of the arthropathies only 5 cases were shown to have objective signs. In one case the knee showed a distinct, symmetrical swelling, in a second the hip-joint, in a third the shoulders were the sites of visible tumescence. Definite hydrarthrosis was present in two cases, both the knees being affected in one and both ankles in the second. In one case there was marked swelling of both knees without any subjective disturbance. In all of the cases studied prompt amelioration took place as soon as efficient treatment had been begun.

The periosteal node and early arthralgia may be looked upon as relatively superficial syphilides and rapidly amenable to treatment. The involvement of the medulla of the bone, however, must be regarded much in the same light as a severe visceral syphilide comparable, perhaps to the involvement of the spleen. It is not at all unlikely that spirochetal "rests" occur in the marrow of the long bones from such early implantation. Such rests may well serve as distributing foci of the later sequelæ, not only in the bones themselves, but possibly such foci serve as depots from which under the influence of either trauma or other factors, the circulation is recharged with spirochetes.

From our studies we conclude that the skeletal structures offer no exceptional barrier to objective or subjective involvement in early syphilis. The apparent and relative infrequency of their occurrence is easily found in the fact that ambulatory cases of syphilis are seldom examined with regard to the bony structures.

The rapidity with which the more superficial lesions disappear under appropriate therapeutic measures justifies the conclusion that such involvement adds nothing to the seriousness of the early symptom-complex.

Those cases, however, in which deep, non-localized pain occurs, without objective findings, probably constitute more serious involvement. They require more vigorous treatment for their disappearance, and must be regarded as an invasion of the bone marrow itself.

The frequent association of the osseous system with involvement of all the other systems would seem to indicate that there is no justification for assuming an osteotropic strain of the infecting organism.

From the stand-point of differential diagnosis the early syphilitic bone and joint manifestations offer no great difficulties. The most important diagnostic features seem to be the presence of pain during the periods of repose.

A CASE OF MULTIPLE MYELOMATA, WITH A DISCUSSION AS TO ITS NATURE AND ORIGIN.*

By B. M. Vance, M.D.,

PATHOLOGICAL LABORATORY, BELLEVUE HOSPITAL, NEW YORK CITY.

(From the Department of Bellevue and Allied Hospitals Charles Norris, M.D., Director.)

INTRODUCTION.

V. Rustizky,[61] in 1876, was the first to apply the term "multiple myelomata" to a case of primary multiple tumors of the skeleton, which he believed arose from the blood-forming cells of the bone marrow. Since that time many different types of multiple bone-marrow tumors have been described under this name of "multiple myelomata," and the condition is now recognized as a definite pathological entity. There is still uncertainty and lack of unanimity in regard to the true classification of these tumors, although the majority of observers are agreed that they are derived from the blood-forming cells of the bone marrow and are related to the primary diseases of the lymphatic-hemapoietic apparatus.

CLINICAL AND PATHOLOGICAL FEATURES OF MULTIPLE MYELOMATA.

The clinical and pathological pictures of the cases of multiple myelomata which have been described are very similar. The disease is one of adult life, over 60 per cent. of the cases occurring between the ages of forty and sixty; 26 per cent. over sixty years,

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* I am greatly indebted to Dr. Charles Norris, at whose suggestion this work was undertaken, and to Drs. Van Horne Norris and William K. Draper, through whose courtesy the publication of the clinical notes on the case was made possible.

and only in a very few cases was the age below forty; 76 per cent. of the cases occurred in men and 24 per cent. in women of the poorer classes. The cases described by Nothnagel[53] and Israel[36] were both young males† of twenty-four and twenty-six years of age respectively, but we have reason to believe that these were not multiple myelomata.

The cases of multiple myelomata all show involvement of the skeleton by tumors which arise primarily from the bone marrow. The bones usually involved are those of the axial skeleton, vertebræ, sternum, and ribs, less often the skull, and the bones of the extremities. The neoplasm, for the most part, has been described as a soft, gelatinous, vascular growth, red or reddish gray in color, in which dark red hemorrhagic areas are common. In other cases the color has been raspberry red, reddish violet, brownish red, yellow, gray, and white. The tumor is confined to the bones, and in only a few instances has it been described in extraskeletal situations. It entirely replaces the normal red bone marrow in the involved areas, and has a corroding action upon the bony tissues themselves. Occasionally it has occurred as circumscribed grayish nodules in the midst of the normal marrow, causing only slight destruction of the osseous tissue.

The involvement of the skeleton renders the bones fragile and gives rise to many characteristic deformities. The vertebral column most often shows an angular kyphosis, due to the destruction of the vertebral bodies in the dorsal and lumbar regions. The sternum, also, presents various grades of deformity, from a simple bowing to an S-shaped curve, which is most marked when accompanied by a kyphosis. Tumor masses of soft consistency may project from either the anterior or posterior surfaces of the sternum, and in the case of Lubarsch,[45] such a mass had apparently been separated from the posterior surface of the sternum and lay free in the tissues of the mediastinum. The ribs usually show fusiform swellings near their costovertebral and costochondral junctions. Occasionally tumor masses have been found in the bones of the skull, pelvis, and the extremities of the long bones, but have caused no characteristic deformities in these situations. Spontaneous fractures are common and occur most frequently in the ribs and less often in the bones of the extremities.

Prominent symptoms of the disease are pain and tenderness to pressure, which are referred, as a rule, to the bones most frequently involved, namely, the ribs, the bones of the extremities, and the vertebræ. The pain is persistent and deep-seated, and becomes more intense whenever the part is moved, either actively or passively. When the involvement is at all extensive, the pain may be so severe as to confine the patient to bed. The patients also suffer from neuralgic pains, referred to the internal viscera, which Parkes Weber[90] believes are caused by compression exerted by the kyphotic vertebral column on the posterior nerve roots in the intervertebral foramina. Some cases, especially in the later stages of the disease, develop a severe secondary anemia, and become markedly emaciated. The number of erythrocytes varies from 3,000,000 to 4,000,000, while the hemoglobin estimation is from 50 to 80 per cent. The leukocyte count is almost always low, varying from 7000 to 15,000, while the differential count shows the normal variations. In no case have any myelocytes been found in the circulating blood. There were many nucleated red cells in the case of Jochmann and Schumm,[38] while in Ellinger's case[19] the anemia was the dominating feature of the disease, and was of the primary pernicious type.

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† Schridde in Aschoff's Lehrbuch, 1913 edition, shows an illustration of a femur of a twenty-year-old male which he diagnoses as a "multiple erythromyeloblastome." There is nothing in the text to indicate that the tumor belongs to the multiple myelomata.

The patients in several instances have developed symptoms of a myelitis transversa with paraplegia, incontinence of urine and feces, etc. This has been found at autopsy to be due to pressure exerted on the spinal cord by the deformed vertebral column.

Other symptoms have been recorded, but these are not typical of multiple myelomata, and are rather due to general exhaustion or some complication. The disease usually runs a chronic course of from six months to two years. In many cases lobar pneumonia is the terminal condition.

A few cases of multiple myelomata have shown tumor tissue, similar to the neoplasm in the bones, present in other parts of the body, as in the left inguinal lymph nodes of the case of Scheele and Herxheimer;[63] in the iliac lymph nodes of the case of Charles and Sanguinetti;[13] in the liver of the case of Hoffmann;[34] in the ovaries of the case of Herrick and Hektoen;[30] on the cricoid cartilage of the case of v. Verebely.[83] The significance of these extraskeletal tumor growths will be discussed later.

There are no secondary pathological changes which can be considered characteristic of multiple myelomata. A few cases have been reported, in which amyloid changes were present in some of the viscera (cases of Heuter[35]); Parkes Weber;[89] H. Weber;[88] O. Pertik.[57] In three cases, those of Bender,[7] Scheele and Herxheimer,[63] Tschistowitsch and Kolessnikoff,[81] deposits of calcium salts were found in the viscera. In the last-named case the deposits resembled the "chalk metastases of Virchow," and were present in the lungs, kidneys, spleen, stomach, heart muscle, and liver.

Another phenomenon, which is observed very often in cases of multiple myelomata, is the presence of Bence-Jones protein in the urine. This is considered by some observers (Kahler,[40] Parkes Weber,[89] Moffat, and others) to be pathognomonic of the disease. Its significance will be discussed in another section.

THE MICROSCOPIC CHARACTERISTICS OF MULTIPLE MYELOMATA, WITH SPECIAL REFERENCE TO THE PLASMA CELL TUMORS.

While the clinical and pathological features of the cases of multiple myelomata are remarkably similar, a variety of types have been distinguished on the basis of the histological characteristics of the tumor cells. There is no doubt, however, that these cells, diverse as they are, are derivatives of the undifferentiated cell of the bone marrow or the myeloblast, which is the ancestor of both the leukocyte and the erythrocyte. The cells of the myelomata always resemble certain elements of normal marrow, and in several cases, such as the one of v. Verebely,[83] where the line of demarcation between normal marrow and tumor tissue was found to be slight, many tumor cells were found in the normal marrow.

The myelomata are composed of large spherical or polyhedral cells which lie without definite arrangement in a fine connective-tissue stroma, separated from each other by a formless ground substance. The stroma contains many thin-walled vessels, most of which are composed of only one layer of endothelial cells. Hemorrhages are prone to occur from the bursting of these vessels, in which case red blood corpuscles lie among the tumor cells. The neoplasm, however, may have a very poor vascular supply, though areas of necrosis are rare in any portion of the tumor. Bone is hardly ever found in the new growth because of the destructive or lytic action of the tumor cells. The cases of Bender,[7] Winkler,[95] Ellinger,[19] Jochmann and Schumm,[38] Scheele and Herxheimer,[63] v. Rustizky,[61] Permin[56]—case 1—showed many giant cells or osteoclasts, and it is possible that they may have contributed to the destruction of the bone.

Five different types of multiple myelomata have been distinguished in the literature on the basis of the morphology of the tumor cell. There is first of all the type which is composed of cells resembling the myeloblast. This is a large spherical cell about the size of a large lymphocyte with an abundant, non-granular, lightly basophilic cytoplasm and a large vesicular nucleus. The nuclei are either centrally or excentrically placed, stain weakly basophilic, and possess a fine filamentous chromatin network, in which lies the acidophilic nucleolus. Cases which belong to the group have been described by v. Rustizky,[61] McCallum,[46] Zinninger,[98] Vignard and Gallavardin,[85] Hart,[29] Permin,[56] Jellinek,[37] Tschistowitsch and Kolessnikoff,[81] Shennan[70] and others.

A second class are formed by those cases whose cells have the size and appearance of the ordinary small lymphocyte. This type was designated by the earlier observers as a lymphosarcoma or pseudoleukemia confined to the bones. Cases of this kind are described by Zahn,[97] Kahler,[40] Herrick and Hektoen,[30] Pertik,[57] Scheele and Herxheimer,[63] Ellinger,[19] Parkes Weber[90] and others.

A third group of multiple myelomata are composed of cells whose cytoplasm contains neutrophilic granules. These may be regularly distributed as in the normal neutrophilic myelocyte, or the cells may contain huge and irregularly shaped pigment clumps. Parkes Weber[89] considers that such cells are atypical derivatives of the neutrophilic myelocyte. Cases of this sort were described by Winkler,[95] Saltykow,[62] C. Sternberg,[74] Parkes Weber,[89] Lubarsch,[45] Herz.[32]

The fourth group is represented by the case of Ribbert,[59] in which the tumor cells differed from those of any other case of multiple myelomata, in that they contained hemoglobin, and thus resembled erythroblasts. He called the tumor an erythroblastoma, and claimed that all stages of the formation of the nucleated red blood cells were present in the tumor growth. Up to the present time no other case of this kind has been described in the literature.

The fifth group is known as the "plasmocytomata," and is composed of those cases whose cells were described as morphologically similar to the plasma cells of Unna and v. Marschalkó. This cell is irregularly oval in shape and about the size of a large lymphocyte. Its protoplasm takes a deep basophilic tint in its peripheral portion, but shows a clear space around the excentrically placed nucleus. The latter is vesicular in type, shows dark chromatin clumps arranged peripherally just within the nuclear membrane, and contains an intensely staining acidophilic nucleus. Cells of this definite morphology were first described by Unna in 1891, in sections of lupus, and called by him "plasma cells," from their supposed resemblance to the "plasma cells" described by Waldeyer in normal testicles.

Since that time plasma cells have been found in the normal intestinal submucosa, spleen, bone marrow, and lymphatic tissues, and in many inflammatory processes, especially of the tongue and kidney (acute interstitial nephritis of Councilman). Many observers have regarded the cell as inflammatory in nature, but they have been unable to determine its origin or mode of development. Unna looked upon the plasma cell as a product of the fixed connective-tissue cells. V. Marschalkó considered it a derivative of the small lymphocyte, basing his theory on the prevalence of plasma cells in inflammatory areas where lymphocytes were especially numerous. Marchand regarded the plasmocytes as descendants of the "klasmocytes," or the cells in the adventitial coat of the smaller blood-vessels. None of these theories are capable of proof.

Elements morphologically resembling plasma cells have been described as the tumor cells in a great variety of cases. These include a large number of small isolated tumors of the uvula and eyelids, and conditions which possess the pathological features of lymphomata, pseudoleukemias, or lymphatic leukemias (cases of Gluzinski and Reichenstein,[23] Ghon and Roman,[99] Maresch, Vogt, and others). Many cases of multiple myelomata have been regarded as plasmocytomata, among which are those of Wright,[96] Christian,[14] Hoffman,[34] Berblinger,[8] Aschoff,[2] Parkes Weber and Ledingham,[91] v. Verebely,[83] Warstat.[87] These observers consider that the tumor cells are derived from the "plasma cells," in the bone marrow, and Berblinger[1], applying v. Marschalko's theory to multiple myelomata, suggests that they arise primarily from the bone-marrow lymphocyte.

The plasma cell, as a matter of fact, is purely a morphological entity and little is known concerning its origin, mode of development, or function. Cells, resembling it, have been described in inflammatory processes, and it is possible that they have a specific role in inflammation, which, however, is still poorly understood. There are, also, many tumor formations composed of cells of "plasma-cell" morphology, and their exact status is uncertain, because such neoplasms can only be classified on their morphological characteristics without regard to embryological considerations. It is especially misleading to speak of certain multiple myelomata as "plasma-cell tumors," not only because the relationship between the plasmocyte and myeloblast is so indefinite, but because many such plasmocytomata are composed of elements quite unlike the "plasma cell" of Unna and v. Marschalkó.

A few cases of multiple bone tumors have been described which resembled multiple myelomata in their clinical course and at autopsy, namely, Seegelken's chondrosarcoma,[68] Marckwald's endothelioma of the bones,[49] and the peculiar case of Devic and Beriel,[17] about which no positive statement was made. The microscopic examination of these cases showed that while the tumors sprang from the bone marrow they were not derived from the myeloid cells proper, and were consequently not multiple myelomata.

CASE.

The patient, George McK., aged fifty-four years, a window dresser by occupation, was admitted to the service of Dr. Draper, in the medical ward of the first division of Bellevue Hospital, January 26, 1912. Seven months before his admission he complained of pain in his neck and ribs. The pain was constant and dull in character, and was increased by motion. The symptoms gradually became more severe, and he was forced to take to bed about two months after the onset of the disease. His previous medical history and that of his family history was negligible.

On admission, physical examination showed a well-nourished but poorly developed man of late middle life, who lay quietly in bed, complaining of stiff neck and pain in the sides. The examination was otherwise negative. On January 29, 1912, an ill-defined tumor, tender to pressure, was discovered in the right anterior triangle of the neck, and attached, apparently, to the bodies of the cervical vertebræ. It increased progressively in size, and by June had assumed the consistence of bone. The patient's condition from June to September improved to such an extent that he was allowed to walk around the wards, though still complaining of pain and stiffness in his neck.

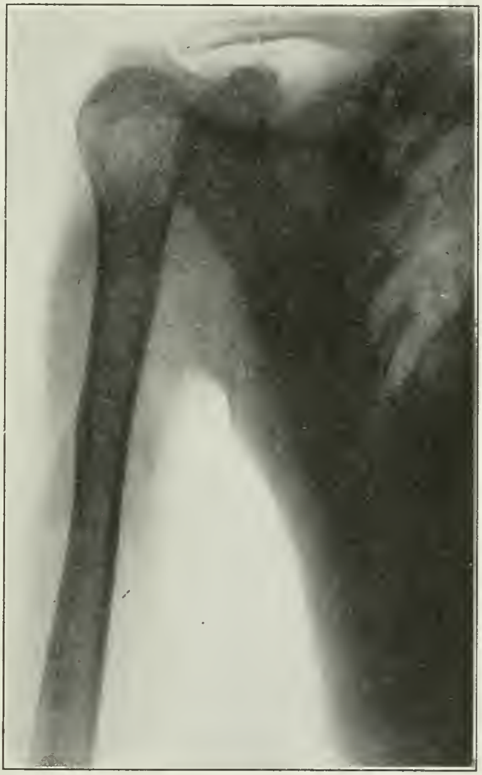

FIG. 1.—Right arm and chest.

Physical examination on September 20, 1912, was as follows: The lambdoid suture of the skull was more prominent on the left side than on the right. The head was held forward with the chin slightly depressed. Rotation of the head was limited to 20 degrees to the right and 30 degrees to the left, because of the pain and physical obstruction. The manubrium sterni was prominent. The ribs were thickened at the costochondral articulations, but none showed crepitus or abnormal mobility. The thigh at the level of the greater trochanter was much larger on the left side than on the right. There was no tenderness or loss of motion in the back, but there was a slight kyphosis present, and the lumbar spines were quite prominent. The general condition of the patient was hardly changed at all.

In October pain in the neck became much worse and the patient gradually grew weaker, so that he had to go to bed. He died October 26, 1912, seven months after admission, on the service of Dr. Norris, the duration of the disease having been fourteen months.

The radiographic examination on February 23 showed areas of rarefaction in the left clavicle, right humerus, right scapula, greater trochanter of the right femur, ribs, upper cervical vertebræ, and the small bones of the hands.

The blood examinations showed a slight secondary anemia. The examination on August 27 revealed erythrocytes, 5,200,000. Hemoglobin, 72 per cent.; leukocytes, 5000; polymorphonuclears, 73 per cent.; lymphocytes, 26 per cent.; transitionals, 1 per cent. No myelocytes or abnormal cells were found in the blood at any time.

January 27 the urine was clear, amber in color, specific gravity 1029, acid in reaction and without glucose, indican, or bile pigment. January 31 the Bence-Jones protein was found in the urine. It was found both early and late in the disease, and in very large amounts, forming a heavy, brownish, sticky, peptone-like mass adhering to the stirring rod. The substance had all the characteristics of the Bence-Jones protein.

Clinical Diagnosis. Multiple myelomata.

The autopsy was performed by Dr. Norris on October 26, within an hour of the patient's death.

The anatomical diagnosis was multiple myelomata, lobar pneumonia, double adhesive pleuritis, chronic congestion of the kidneys, parenchymatous hepatitis, suppurative otitis media, and sphenoiditis.

Body was that of an elderly male adult, 176 cm. in height, very pale and emaciated.

Lungs: The lungs were congested and edematous. The upper lobe of the right lung was consolidated, showing a lobar pneumonia in the stage of red hepatization. The pleural surfaces were everywhere firmly adherent to the chest wall by fibrous adhesions. The bronchi were normal. The bronchial lymph nodes were small and anthracotic.

Heart: The heart was normal in size. The valves were normal, except that one of the pulmonary cusps was very large and fenestrated, and the left and middle aortic cusps were adherent near their edges. The musculature was dark red in color and showed no fibrosis. The coronary arteries were normal. The upper part of the aorta was normal, but the lower part of the adbominal portion showed a commencing sclerosis.

Peritoneum: The peritoneum was normal, except for an adhesion between the duodenum and the gall-bladder.

Gastro-intestinal tract: Normal.

Liver: The liver weighed 1840 grams. It was dark red in color, and had a cloudy appearance on section. The gall-bladder was normal and distended by black tarry bile.

Spleen: The spleen weighed 100 grams. The capsule was normal. The splenic pulp was pale red in color, and showed many fibrous septa.

Suprarenals: Apparently normal.

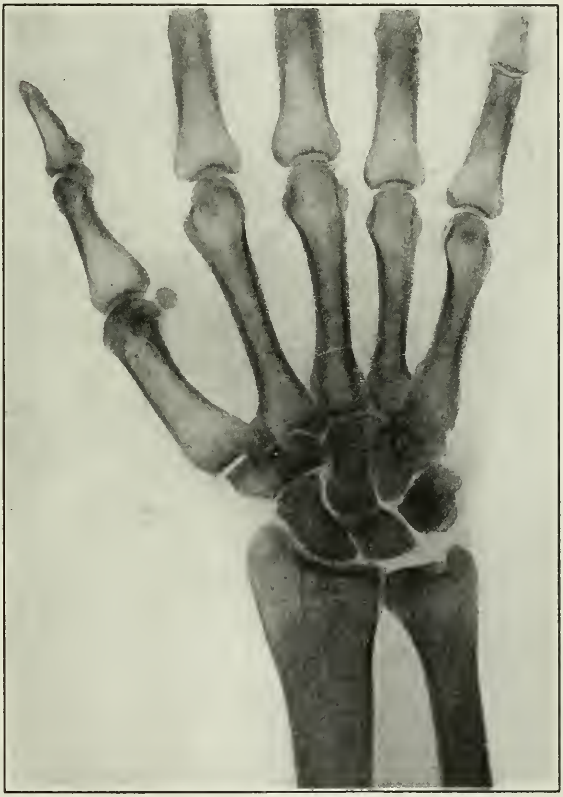

FIG. 2.—Right hand.

Genito-urinary tract: The kidneys were large and congested, and weighed about 475 grams. They were firm. The capsule stripped off readily, leaving a smooth surface on which were a few small cysts. The cortex was thickened and its markings indistinct. The pelves, ureters, and urinary bladder were normal.

The prostate was enlarged, and in both lateral lobes were two large foci of increased firmness. There was a double hydrocele, the one on the left side being larger than the one on the right. The testicles and epididymes were normal.

Organs of the throat and neck: These were normal.

Head: The scalp, the meninges, and the brain were normal. The left middle ear was normal, while the right middle ear and sphenoidal sinuses contained a considerable amount of thin whitish pus.

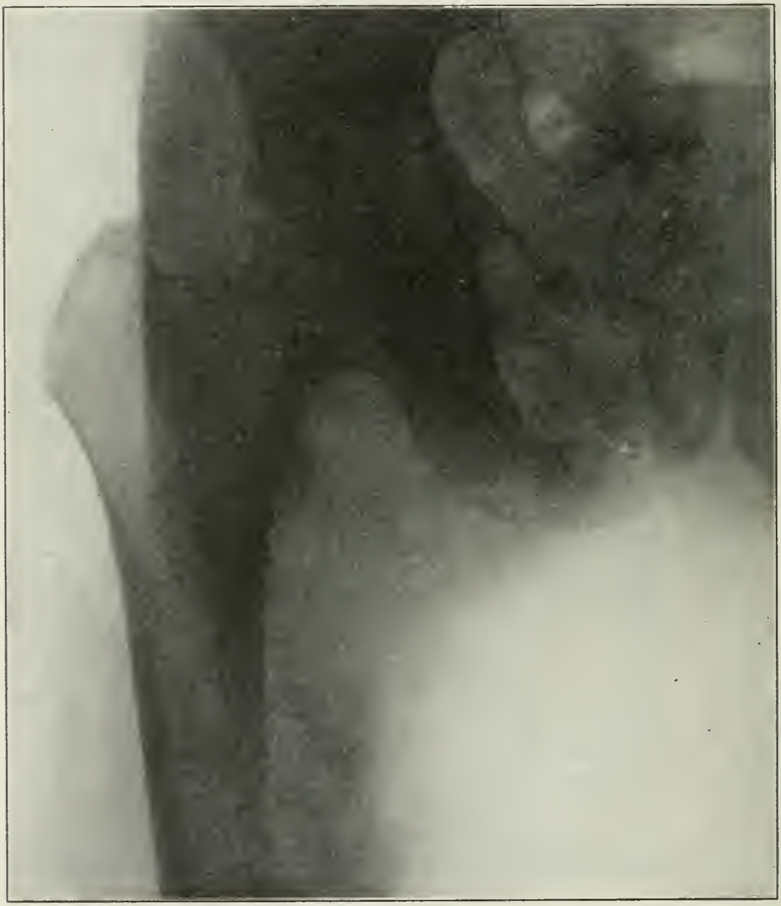

Fig. 3.—Right hip and pelvis.

Skeleton: The bones of the skeleton were extensively infiltrated by a neoplasm, yellowish white in color, in consistency like jelly, and homogeneous in appearance, resembling a rapidly growing round-cell sarcoma. The growth was in many places the seat of hemorrhages which gave it the dark red appearance of freshly clotted blood. The cancellous bone had entirely disappeared in the regions occupied by the neoplasm, and the periosteal layer also was thinned out by the growth.

The bodies of the cervical vertebræ were almost entirely replaced by the tumor tissue, and some of the intervertebral cartilaginous disks showed granular degeneration and softening. The tumor mass in the neck projected from the anterior surface of the bodies of the cervical vertebræ and infiltrated the adjacent soft tissues. It extended from the basilar portion of the occipital bone to the superior thoracic opening. A few of the dorsal and lumbar vertebræ were found to be infiltrated with tumor tissue, and there was a slight kyphosis present in the lumbar region. Thorough investigation of the vertebral column, however, was impossible.

Externally, the anterior portion of the chest wall was depressed, the ribs were bowed, and displayed numerous fusiform swellings composed of hemorrhagic tumor tissue, surrounded by periosteum. The largest of these swellings was about the size of a chicken's egg. They were situated near the costochondral junction and projected into the pleural cavity, carrying before them the thickened pleural membrane.

The sternum was everywhere infiltrated by hemorrhagic, neoplastic tissue, but, except for a marked increase in thickness, showed no special deformity. The lower end of the right femur contained a small red area of tumor formation, say 2 x 1 x 1 cm. The entire upper half of the right femur was infiltrated by soft, white tumor tissue, containing large, dark red hemorrhagic areas. The clavicles also showed focal areas of tumor infiltration. The other bones of the body were not examined at autopsy.

The neoplasm was entirely confined to the skeleton, and no tumor tissue was found in the other viscera. The tumors showed no tendency to infiltrate into the soft parts around the bones except in the anterior portion of the neck. The anatomical characteristics of the tumor indicated that it was a multiple primary neoplasm of the red bone marrow.

Microscopic Examination. The viscera, upon microscopic examination, showed but few noteworthy changes. Sections of the upper lobe of the right lung presented the typical picture of pneumonic consolidation. The rectus abdominalis muscle was the seat of a marked Zenker's degeneration.

The liver showed marked parenchymatous degeneration. The spleen contained a few focal necroses. The kidneys were the seat of a slight chronic parenchymatous nephritis and passive congestion. The left kidney contained a small fibroma situated in one of the pyramids. The other viscera were practically normal.

Pieces of the tumor were fixed in formalin, Orth's and Zenker's fluid. Absolute alcohol was not employed. The imbedding was in celloidin, and the sections were stained with hematoxylin and eosin, with Wright's stain, Jenner's stain, Unna's methyl-green pyronin stain, Ehrlich's triacid stain, Butterfield's[163] eosin-thionin stain, Mallory's anilin-blue connective-tissue stain and Mallory's phosphotungstic acid hematoxylin. Smears were made from the fresh tumor tissue, but from them nothing was gained. The oxydase test was made by Prof. William G. McCallum, and was negative.

The sections of the tumor from the neck, the ribs, and the head of the femur were found to be similar in their microscopic structure. The stroma was composed of a very fine and quite cellular connective tissue, with a moderate number of delicate bloodvessels, which in some places consisted of a single layer of endothelial cells. The tumor cells lay closely packed, but separated in some places by an eosinophilic ground substance in the form of small globules. The sections taken from the hemorrhagic area showed numerous erythrocytes between the tumor cells. No tumor cells were found in the lumen of any of the bloodvessels.

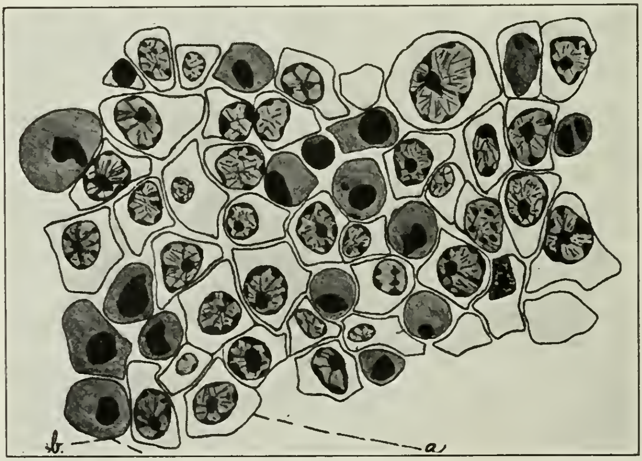

FIG. 4.—Drawing of a section from tumor in cervical vertebræ. (*a*) tumor cell of the myeloblast type; (*b*) tumor cell with pyknotic nucleus.

The tumor cells were of several types. The most numerous was a large spherical or polyhedral cell of slightly basophilic protoplasm, surrounding a large vesicular and excentrically placed nucleus. This nucleus contained several dark blue chromatin clumps, arranged against the nuclear membrane, a fine filamentous chromatin network, and an intensely staining acidophilic nucleolus. No granulations of any kind could be demonstrated in the cell protoplasm. This cell had the appearance, size, and general staining reactions of the ungranulated cell of the bone marrow, the common ancestor of the granulated myelocyte and the nucleated red cell.

Another type was a cell with a solid dark blue, pyknotic nucleus, excentrically placed, and an eosinophilic protoplasm, which at first, was held to be due to the presence of hemaglobin (Norris and Vance[52]). These cells varied in size from a small lymphocyte to that of the cell described with the basophilic protoplasm and vesicular nucleus. They had a close resemblance to normal erythroblasts until it was found on high magnification that the protoplasm did not stain diffusely. The stain occurred in the form of irregular eosinophilic clumps, which were composed of small globules about the size of a nucleolus. In many cells, single globules of this type were found just outside the pyknotic nucleus, and surrounded by a clear space in the midst of the eosinophilic protoplasm.

Cells which appeared to be transitional forms between the above types were also seen. Their cytoplasm stained all gradations from a light basophilia to a complete eosinophilia. Their nuclei showed all intermediate stages from the vesicular type to that of complete pyknosis, while others displayed different varieties of karyorrhexis. The impression was given that there existed an active process of degeneration among the tumor cells.

SUMMARY OF CASE.

At autopsy there was found a multiple primary neoplasm of the bone marrow, extensively infiltrating the ribs, cervical vertebræ, clavicles, sternum, and femur. The tumor tissue caused destruction of the bone, wearing away the cortex to a thin layer and entirely replacing the cancellous bone. The neoplasm was confined to the osseous system, the viscera were not involved nor were the surrounding soft tissues infiltrated, except in the neck. The tumor was yellowish white in color, soft in consistency and homogeneous in appearance, resembling a rapidly growing round-celled sarcoma. The masses in the sternum and the head of the right femur showed extensive hemorrhages, which gave the neoplasm a dark red appearance like clotted blood.

On microscopic examination the tumor cells were found packed together in a stroma, consisting of very fine cellular connective tissue, delicate bloodvessels, a fine eosinophilic ground substance, and red blood cells whenever the section was taken from a hemorrhagic area.

It is plain that the tumor cells in this case all took their origin from the cells of the bone marrow. The large cell with the basophilic cytoplasm and the large vesicular nucleus was morphologically very similar to the myeloblast of the bone marrow. The cell with the irregularly staining eosinophilic protoplasm and pyknotic nucleus was not so easy to identify, though it was quite evident from the presence of transitional forms that it must have been derived from the myeloblast type. Its existence can be explained in two ways:

1. The neoplasm is an erythroblastoma, as described by Ribbert,[59] in which case the cell is a nucleated red cell and the process in the tumor is erythroblast formation. The objection to this theory is that the tumor elements with the pyknotic nuclei take the eosin stain irregularly and not diffusely, and are consequently not normal

erythroblasts. On the other hand, they may be regarded as an atypical form of the nucleated red cell in which the protoplasm manufactures hemoglobin in an abortive fashion. The substantiation of this theory depends on the demonstration of hemoglobin in the cytoplasm, and that was impossible from the material at our disposal in this case.

2. The neoplasm can be considered as a myeloblastoma, in which occur different stages of cell degeneration and disintegration. If we accept this theory we must regard the eosinophilic material in the cytoplasm as distinct from hemoglobin, because hemoglobin never occurs in a cell unless it is manufactured by the protoplasm or else acquired by the phagocytosis of normal erythrocytes. The first possibility would give the cells the dignity of erythroblasts, while the second view is not tenable in this case, because there is no phagocytosis present in the tumor. Christian[14] advanced the theory that the degenerating tumor cells have the power to imbibe the soluble hemoglobin in the tissues, but this idea is erroneous. Besides, degenerating protoplasm is invariably acidophilic, and the eosinophilia can be explained on the grounds of cell disintegration.

This case is not identical with any other case described in the literature, though it has many points of similarity with those described by Ribbert,[59] McCallum,[46] Wright,[96] Parkes Weber,[89] Christian,[14] Permin.[56] It is difficult to decide whether to classify the tumor as an erythroblastoma showing the formation of atypical erythroblasts, or as a myeloblastoma showing numerous cell degenerations. It is certain that the large cells with the vesicular nucleus are derived from the myeloblast of the bone marrow, but further differentiation is not possible because of our lack of knowledge concerning the significance of the other cell forms in the tumor.

A CONSIDERATION OF THE RELATIONSHIP OF THE MULTIPLE MYELOMATA TO THE DISEASES OF THE LYMPHATIC-HEMAPOIETIC APPARATUS.

A short review of bone-marrow formation is necessary for a comprehensive conception of the different primary affections of the lymphatic-hemapoietic apparatus.

Maximow described the migration of the undifferentiated star-shaped cells and newly formed bloodvessels from the perichondrium into the prebony cartilage as the beginning of blood formation in the skeleton. The star-shaped cells developed into two primary forms: (1) the fixed supporting cells which linked themselves together by long processes, and (2) the spherical "Wanderzellen" or myeloblasts. The bone marrow at this stage resembles lymphatic tissue so markedly that it is known as "lymphoid marrow." Later, the fixed supporting cells develop into the osteoblast, osteoclast, and the reticular cell of the marrow, while the myeloblasts become differentiated into the various blood-forming elements, as the erythroblast, the granulated myelocytes, the small lymphocyte-like cells, and the megakaryocyte.

Now the morphology and genesis of the lymphoblasts, the "Wanderzellen" of lymphatic tissues, is very similar to that of the myeloblasts, but their future development is not, as the lymphoblast develops under normal conditions into a single cell form the small lymphocyte. However, it is a well-known fact that myeloid cells very often appear in lymphatic tissues in many pathological processes, such as the myelogenous leukemias and the severe anemias, and conversely lymphocytes occur in the bone marrow in lymphatic leukemias and pseudoleukemias. The consensus of opinion is that such aberrant elements develop from cells normally present in these situations, which suggests that the myeloblast and lymphoblast are closely related though not absolutely identical.

The above embryological considerations offer a basis of classification and a reasonable explanation for the variety of primary neoplasms which occur in the bone marrow. They are divided into two main groups. The first group take their origin from the fixed supporting cell of the embryonic bone marrow, and include the benign connective-tissue tumors, the endotheliomata, and the ordinary malignant sarcomata. The second group are derived from the primary mesenchymal "Wanderzellen," and are classified under the title of "Primary Diseases of the Lymphatic-hemapoietic Apparatus." These tumors are peculiar, pathologically, in that the neoplastic tissue pervades the body as a diffuse infiltration, or in the form of discrete nodules; but it is only found in situations where lymphoid and myeloid tissues are normally present. The tumors are primary hyperplasias of some single derivative, or group of derivatives, of the lymphoblast or myeloblast at each separate situation rather than metastases in the sense of the word as applied to malignant sarcomata. The tumor cells can also be demonstrated in the circulating blood in some forms, namely, the leukemias, while in others, as the pseudoleukemias, the blood is free of these elements. This fundamental difference has never been explained satisfactorily. It is evident, however, that the primary diseases of the lymphatic-hemapoietic apparatus show definite characteristics not possessed by other tumor groups, but which are explainable by the close embryological relationship of the lymphoblast and myeloblast.

The tumor cells of most of the members of this group are easy of identification, and such neoplasms can be readily classified. There are, however, isolated cases described where the pathological features indicated that the neoplasm was a member of the lymphatic-hemapoietic group, but where the embryological status of the tumor cells could not be definitely determined. These cases must remain, therefore, as unknown quantities in any scheme of classification. The numerous "plasma cell tumors" and the case described by

Norris[51] as a "Multiple Systemic Sarcoma of Myelogenous Origin" are examples of such neoplasms. Until the nature and origin of the tumor cells can be definitely determined a comprehensive classification of the lymphatic-hemapoietic group of diseases will be difficult.

The pathological characteristics of the multiple myelomata, however, put it without question in this group of diseases. In addition, the limited distribution of the tumor growth, which is confined to the skeleton in all save a few instances, and the marked resemblance of the tumor cells to the different bone-marrow elements, suggests that the neoplasm is composed of myeloblasts or derivatives of myeloblasts. Lubarsch[45] plausibly explains the rare cases of extraskeletal myelomata in the liver and lymph nodes by suggesting that such tumors were derived from aberrant myeloid tissue present in those situations.

The different types of multiple myelomata which have been described in the literature have been divided into the following five groups:

1. The myeloblastoma, composed of myeloblasts.
2. The myelocytoma, composed of myelocytes containing neutrophilic granulations.
3. The erythroblastoma, composed of nucleated red cells.
4. The lymphocytoma, composed of cells resembling lymphocytes.
5. The plasmocytoma, composed of cells of "plasma-cell" morphology.

Of the five types the plasmocytoma cannot be regarded as a true myeloma for reasons which we have already discussed. The lymphocytoma is a distinct tumor type, but it cannot be separated from the pseudoleukemias and lymphosarcomas, which involve only the bones, many of which have been described in young individuals. The tumor cells of many of these cases are probably not derived from the myeloblast, and it is very questionable whether they should be classified as true myelomata. The myelocytoma and erythroblastoma are theoretically multiple myelomata, but until more examples of such tumors have been described, they must be included in the classification with reservation. The myeloblastoma is the only one of the five which is unquestionably a well-recognized pathological entity, and in the present state of our knowledge the multiple myelomata term should be reserved for multiple bone-marrow tumors of myeloblastic origin.

BENCE-JONES ALBUMINURIA.

The peculiar body known as Bence-Jones protein was first described by Bence-Jones in 1846 in the urine of a patient of MacIntyre's. He found that a thick yellowish precipitate occurred, when the urine was heated to about 50° C., but that this precipitate dissolved completely on boiling and reappeared when the solution was cooled. The full significance of this protein in the urine, which had different reactions from those of the ordinary urine albumin, was not recognized at that time, because the case was regarded simply as "mollities ossia rubra."

In 1876 v. Rustizky described his case of multiple bone tumor, to which he gave the name multiple myelomata. The urine examination was apparently normal, and no record was made of the presence or absence of the Bence-Jones protein. It was not until 1889, when Kahler reported a similar case, in which Bence-Jones protein was found in the urine, that any association was drawn between this finding and the disease. Since then many observers, especially the Italians and English, have accepted his conclusion that multiple myelomata and the Bence-Jones protein are inseparable, and Parkes Weber, Moffat and others exclude all cases from the multiple myelomata group which do not show the Bence-Jones protein in the urine. The specific nature of this reacion has, however, been questioned, and a careful review of the literature shows that while true myelomata may not always excrete Bence-Jones protein, the urine of many other conditions may contain this body with all its characteristic reactions.

A review of the latter group, however, brings out the one important fact that in no case in which the urine contained true Bence-Jones protein were the bones or bone marrow definitely proved to be free of pathological processes. Examples of this point were Askanazy's case of lymphatic leukemia, Weinberger's case of chloroma, Fitz's case of myxedema, Seegelken's case of chondrosarcoma, Raschke's case of senile osteomalacia, and the peculiar case described by Gluzinski and Reichenstein. Frank secondary carcinoma of the bones was present in the cases of Bence-Jones proteinuria described by Decastello and Boggs and Guthrie.[100] It is, therefore, obvious that Bence-Jones proteinuria is not strictly a pathognomonic sign of multiple myelomata, though its frequent association with that condition (80 per cent. of the cases according to Rosenbloom) gives it a considerable diagnostic value.

The tests for Bence-Jones protein are quite distinctive and very simple to perform. The urine is heated slowly and an albuminous precipitate forms at a temperature between 50° and 56° C. On further heating the protein dissolves, disappears completely when the solution is boiled, but as the solution cools the precipitate reforms. The same phenomenon of disappearing on boiling and reappearing on cooling is also shown by the precipitate formed by adding potassic ferrocyanide and acetic acid to the urine, and the precipitate formed in the ring contact test of the urine with strong nitric or hydrochloric acid. The urine also gives a violet color with the Biuret test. There are other tests, but the ones mentioned above are the most used and are sufficient to identify the substance.

The urine in case of Bence-Jones proteinuria usually shows on examination a high acidity, a specific gravity of 1013 and 1020, and a viscidity above the normal. In some cases the reaction was neutral and in one case it was alkaline. In most cases the urine was clear, but in some it was turbid, which Parkes Weber and other English observers claim may be the Bence-Jones protein spontaneously precipitated. In the majority of cases the body was excreted continuously in the urine, though in some no record can be found of this fact. This peculiarity serves to distinguish the true Bence-Jones protein from the albumoses often temporarily excreted in the urine of patients suffering from cachectic or febrile conditions.

The nature of the Bence-Jones protein is not fully understood at present. Some of the earlier writers (Kühne) considered it an albumose, but studies by Moitessier, Magnus-Levy, Abderhalden, and Rostoski and others on the cleavage products obtained from the body by peptic and tryptic digestion, suggest that its composition is more complex than that of an albumose, and more like that of a protein. Abderhalden's theory is that it is a tissue albumin which is manufactured in the organism and takes place in its metabolism, but which is foreign to the blood and is promptly excreted in the urine whenever it enters the blood stream. The experiments of Stokvis, Matthes, and Ellinger have shown that whenever Bence-Jones protein is injected into dogs subcutaneously, intravenously, or per rectum the body is recovered unchanged in the urine. Rostoski was unable to differentiate the Bence-Jones protein from other proteins by the "precipitin reaction." On the whole the researches on its composition have been quite unproductive, and all that we can definitely say is that it is probably an albumin manufactured in the body under pathological conditions, different in composition from any of the other body proteins.

Many theories have been advanced suggesting the origin of the Bence-Jones protein in the body. Magnus-Levy believed that it was an abnormal product of the protein metabolism of the food. Decastello regarded the body as a derivative of diseased kidney epithelium and claimed that it was never found in the urine if the epithelium is normal. Simon, Kühne and Chittenden and Moitessier considered that it was formed by the action of the enzymes of the tumor cells on the proteins in the blood. Parkes Weber looked upon it as a peculiar secretion or degeneration product of the myeloma cells. Rosenbloom endeavored to prove that the body is a cleavage product of osseo-albuminoid, and that its presence, in cases of multiple myelomata, is due to the rapid destruction of bone by the neoplasm. None of these theories have as yet been confirmed.

Many analyses have been made of the organs and body fluids of multiple myelomata cases, and normal cases, with a view to finding out the site of formation of the Bence-Jones protein. Barr, Ribbinck, and Löwe were unable to find the body in the organs of their cases. Fleischer found a substance giving the reaction of Bence-Jones albumin in the bone marrow of a normal individual. Coriat found a similar body in the pleural fluid of a case of multiple neuritis, though the urine was free from the protein. On the other hand, substances with similar properties to Bence-Jones protein have been obtained by Ellinger, Wood, and Parkes Weber from the bone marrow of multiple myelomata; by Askanazy from the bores of his case of lymphatic leukemia, and by Ellinger from the pleural fluid of his case of multiple myelomata.

It is quite probable that the formation of Bence-Jones protein in the body is connected in some way with the pathological changes in the bones. The frequent association of Bence-Jones proteinuria and multiple myelomata, the involvement of the bones in other cases of Bence-Jones proteinuria, and the occasional demonstration of bodies similar to Bence-Jones protein in the diseased bones, suggest this fact. The mode of formation of this body is still unknown, and so is the method by which it enters the blood and is excreted in the urine. At present our knowledge of Bence-Jones protein is rather theoretical, and many more observations will have to be made before any satisfactory conclusion as to its nature can be reached.

CONCLUSIONS.

1. The multiple myelomata are multiple primary tumors of the bone marrow, occurring, for the most part, in elderly individuals, and manifested during life by deep-seated pain in the bones, characteristic deformities of the skeleton, spontaneous fractures in many bones of the body, severe secondary anemia, and emaciation.

2. The presence of Bence-Jones protein in the urine is characteristic of many cases of multiple myelomata, but it is not a pathognomonic sign of the disease, as it is occasionally found in the urine of other bone conditions.

3. At postmortem, cases of multiple myelomata show the presence of soft, homogeneous tumor masses which replace the cancellous tissue of the bones of the trunk, the vertebræ, ribs, and sternum, and less often of the ends of the long bones of the extremities, the diploë of the skull, and the small bones of the hands and feet.

4. The multiple myelomata are confined to the bones, though a few cases have been reported of extraskeletal growths.

5. The multiple myelomata are composed of cells practically identical with the myeloblasts of the bone marrow or their derivatives. Five different groups of these tumors have been described.

   (*a*) Myeloblastoma.
   (*b*) Neutrophile myelomata.
   (*c*) Erythroblastoma.
   (*d*) Lymphocytoma.
   (*e*) Plasmocytoma.

The first three tumor types are true multiple myelomata. The lymphocytoma is a distinct tumor type, but as there is considerable doubt regarding the relation of the tumor cell to the myeloblast, it cannot be unquestionably classified as a true myelomata.

The "plasma cell" tumor cannot be considered as a pathological entity until more is known about the origin and mode of development of the plasma cell.

6. The multiple myelomata belong to that group of tumors which are composed of cells derived from the primary mesenchymal "Wanderzellen," and are closely related to the leukemias, chloromas, and other diseases of the lymphatic hemapoietic apparatus.

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MASSIVE HEMORRHAGES FROM THE STOMACH WITHOUT DEMONSTRABLE ULCER.

By Alexis V. Moschcowitz, M.D.,

PROFESSOR OF CLINICAL SURGERY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY; ATTENDING SURGEON, MOUNT SINAI HOSPITAL; VISITING SURGEON, HAR MORIAH HOSPITAL, NEW YORK.

Early in 1915, within a period of less than one month, I had the opportunity to operate upon four patients, upon whom the unequivocal diagnosis of a bleeding ulcer of the stomach had been made, both by myself and by several very competent colleagues; and yet none of the operations failed to reveal even the slightest tangible lesion of the stomach. In spite of a most unfavorable outlook in all of these cases, and practically a hopeless one in two, all of these patients recovered. The fortunate outcome, while gratifying, leaves me, nevertheless, with a sense of incompleteness of the study of the pathological data, inasmuch as my observations are based only on the examination of the unopened stomach *in vivo* and not on postmortem material. Clinically, nevertheless, these cases are of profound interest, and even with the shortcomings I have mentioned, deserve the fullest report. The histories of these cases are the following:

Case I.—Chas. R. Austrian, aged thirty-six years, was admitted to the Medical Division of Mount Sinai Hospital, upon the service of Dr. Manges, January 7, 1915. His illness was of two and a half years' duration, and began with the vomiting of a large quantity of blood without any premonitory symptoms. This hematemesis continued for a few days and then ceased for three or four months, when he again vomited large amounts of blood during several consecutive days. This cycle was repeated on two further occasions. After the fourth attack the patient entered a hospital in Brooklyn, where he was operated upon. An incision through the upper part of the right rectus was made, but apparently nothing was found to account for the hematemesis; the appendix was removed. The condition of periodic profuse hematemesis was unchanged by the operation. Altogether there had been nine such attacks within two and a half years, each attack lasting several days, so that by the termination of the last attack the patient was profoundly anemic, and anxious to obtain relief, if possible, even by further operation.

The physical examination revealed a systolic murmur over the whole precordium, with accentuation of the second sound. The abdomen showed a peculiar fulness of the epigastrium, with marked local tenderness to the right of the median line; the liver was palpable one and a half fingers below the free border of the ribs. The patient, just having recovered from an attack of hematemesis, was greatly prostrated, emaciated, and apparently very anemic. At no time during his observation at the hospital was blood found in the stomach contents or in the feces. Test meals on several occasions showed, on an average, a total acidity of 85 to 90, and free HCl 50 to 60. Hemoglobin, 63 per cent. Two roentgen ray examinations were suggestive of adhesions around the pylorus, with dilatation and ptosis of the stomach.

I was requested to see the patient by Dr. Manges; we agreed that the patient, in all probability, suffered from an ulcer at the pylorus, with a somewhat atypical symptom-complex, and advised operation.

Operation, January 30, 1915. Five-inch median epigastric incision. The liver was found to be enlarged, as was indicated in the physical examination. It was of a deep purplish color, and soft in consistency; its capsule was wrinkled, not tense. In the region of the cicatrix of the previous operation there were present massive adhesions, which united the omentum, the liver, and the abdominal parietes. These were carefully freed, in order to permit a thorough exploration of the stomach, pylorus, and duodenum. Even the most painstaking examination failed to reveal the slightest suspicion of an ulcer; the only abnormality was a somewhat greater tortuosity of the gastric vessels than is normal. A specimen was removed from the liver for pathological study, and was reported by Dr. F. S. Mandlebaum as "congestion." The postoperative course was marred by pneumonia, but the patient was discharged with a well-healed scar February 13.

I saw and examined the patient October 3, 1915. In the interval there had been no further attack of hematemesis; in fact, the patient vomited only once or twice during that time. The patient is, however, quite dyspneic, and is beginning to suffer more and more from his cardiac trouble.

Epicrisis. Quite properly it might be argued that the primary cause of the hematemesis in this case is to be looked for in the cardiac condition; this caused secondarily the hepatic congestion, which in turn was followed by the gastric hemorrhages. Granted that such is the case, we must, nevertheless, assume a loss of continuity in the gastric mucosa and a subjacent vessel to permit the escape of such large amounts of blood. The only other hypothesis possible is that of hemorrhage per diapedesim, a theory long since disproved. I believe that an ulcer was present, but that it was so small as to escape detection. It is on this account that I include this case in my report.

Case II.—Morris I., Russian, aged thirty-three years, was admitted to my service at Mount Sinai Hospital February 18, 1915. For the past four years the patient had been suffering from pain in the epigastrium, which radiated to the back at about the level of the tenth dorsal vertebra; the pain was relieved by the ingestion of food for a period of one to two hours. Associated with this pain there occurred also vomiting, which ensued about one hour after eating. Very frequently the patient also vomited large amounts of pure blood, followed by tarry stools. The patient felt very weak, and lately had lost seventeen pounds in weight.

The physical examination was entirely negative except for tenderness at McBurney's point and a localized area of exquisite tenderness in the epigastrium to the right of the median line. The report of the roentgen-ray examination made by Dr. Jaches was "duodenal ulcer."

Operation, February 20. A short Sprengel incision through the left rectus was first made, but in order to permit a more thorough examination the incision was extended so as to divide both recti. The stomach was found to be somewhat dilated, but with this exception absolutely nothing of an abnormal nature was found; neither in the stomach, duodenum, gall-bladder, liver, nor pancreas. The appendix was removed and was found to be normal.

After an uneventful convalescence the patient was discharged, with a well-healed scar, March 9.

The next case is perhaps the most interesting of my series:

Case III.—Minnie R., Canadian, graduate nurse, aged twenty-five years, was admitted to the hospital February 14, 1915.

Past History. Typhoid fever nine years ago; about three years ago, while in training school and on night duty, she complained for a few days of a gnawing feeling in the epigastrium after the midnight meal. Test meals taken at that time were negative. Patient was considered a neurasthenic, and never was ill enough to be taken off duty.

February 14, 1915, at 2 P.M., she vomited about thirty ounces of blood, without any premonitory symptoms; at 4 P.M., a like amount of blood was vomited; at 9 P.M., fifty ounces of blood were vomited, and the patient fainted. She was transferred to the hospital and was treated with morphin, rest in bed, and ice-bag to the epigastrium. February 15 the hemoglobin percentage was 47. In the evening the patient again vomited thirty ounces of blood and again fainted. During the next three days there was a cessation of vomiting, but there was continuously melena, and in consequence the hemoglobin percentage dropped lower and lower. Operative interference was considered, but was thought inadvisable on account of the poor condition of the patient.

On February 19 the patient was transfused by the citrate method by Dr. Lewisohn, raising the hemoglobin percentage from 35 to 55 per cent. In spite of this transfusion the condition of the patient became continuously worse. She was so anemic that no accurate measurements of the hemoglobin percentage were obtainable with the Sahli instrument. I therefore decided upon operation.

At midnight of February 20, after a preliminary transfusion by the citrate method by Dr. Lewisohn, 800 c.c. being transfused, the stomach was exposed through a median epigastric incision. All the viscera in the upper part of the abdomen were thoroughly explored, particular attention being paid to the stomach and duodenum. After carefully exploring the anterior wall of the stomach and finding nothing suspicious, the lesser peritoneal sac was entered through the gastrohepatic omentum and the entire posterior wall examined with the greatest care. Absolutely nothing of an abnormal nature was found. In sheer despair I made a posterior retrocolic gastroenterostomy and excluded the pylorus.

On the following day her condition was excellent. There was still some melena, but this could very readily be accounted for by bleeding which had occurred prior to the operation.

Condition of the patient was perfectly satisfactory on my morning visit to the hospital on February 22. At twelve o'clock noon of that day I was hurriedly summoned to the hospital by a message that the patient had suddenly gone into collapse, and was in a moribund condition. An acute dilatation of the stomach was considered to be possible, and I therefore passed a stomach-tube and withdrew over a quart of bright red blood; this was followed by a lavage of the stomach with ice-water until the washings returned clear.

From that time on the condition of the patient began to improve; the hemoglobin slowly increased, and she was discharged well four weeks later.

Epicrisis. The history and course of this case is typical of the "exulceratio simplex of Dieulafoy." The sudden profuse hematemesis without any preceding gastric symptoms is particularly suggestive. The postoperative course is also most interesting. The occurrence of an almost fatal hemorrhage thirty-six hours after operation is very interesting, and will no doubt be regarded by many as proof of the failure of operation. To my mind, however, such an argument is entirely erroneous; at best it may be argued that I selected in this case an indirect method to stop the hemorrhage instead of a direct method. Had the condition of the patient been better I would have incised the stomach and searched for the bleeding-point, with certainly a greater promise of success.

Case IV.—Esther K., had been under hospital observation for more than a year. When admitted the first time to the pediatric service of Dr. Koplik, April 24, 1914, she was two years and three months old. Measles and pneumonia one year ago. Furthermore, it is important to note in the history that five months ago the patient was operated upon at another institution for a congenital dislocation of the hip by the bloodless reduction method, and that the duration of the anesthesia was two hours. On the day following this anesthesia the patient vomited blood for the first time. The symptom recurred four times within the next two days, and then apparently ceased. Four weeks prior to her admission to Mount Sinai Hospital there was another cycle of hematemesis, and again one day before admission. The last amount was 175 c.c. The child has had fever for two days, with profuse sweating; there was present also edema of neck, face, and feet. The last attack of hematemesis was followed by tarry stools.

The physical examination upon admission revealed the following facts worthy of record: (1) a profound anemia; (2) a short systolic murmur at the apex, not transmitted; (3) a congenital dislocation of the left hip.

April 25, 9 c.c. of rabbit serum were injected into the buttock. This was followed in twenty minutes by a universal urticaria and itching, but no cyanosis and no dyspnea; the urticaria disappeared in ten minutes. Patient was profoundly toxic and in a stuporous condition; the pulse became imperceptible and required energetic stimulation.

April 26—Hemoglobin (Sahli)	12	per cent.
Red blood cells	1,689,000	
Leukocytes	10,000	
Polynuclears	62	per cent.
Mononuclears	38	"

A loud murmur, probably hemic in character, was heard at the base. The vomiting of blood continued.

April 29 patient was transfused by Dr. A. Hyman, by the cannula method, raising the hemoglobin from 12 per cent. to 48 per cent. After the transfusion the child appeared to be in excellent condition, was perfectly conscious, and took nourishment well.

The vomiting of blood ceased, and in spite of tarry stools the hemoglobin rose steadily and reached 62 per cent. on May 12. Without any visible bleeding, either from mouth or rectum, there occurred a recession in the percentage of the hemoglobin, so that by June 1 it was only 40 per cent. The general condition of the patient, however, was much improved, and the child was discharged June 20, 1914, at the request of the mother.

Patient was readmitted June 25, 1914, or five days later. Since her discharge from the hospital the condition had rapidly deteriorated; the anemia rapidly became worse, and the face and neck were becoming more puffy. The mother stated that the child had had several tarry stools. On the day preceding the readmission to the hospital the child vomited blood, and there was also melena. June 26 the hemoglobin percentage was only 22, with a red blood cell count of 2,150,000. For a long time thereafter citrate of iron was administered hypodermically. Several attempts were made to obtain a satisfactory test meal, but they were not successful until July 17, when 10 c.c. of partly digested, non-odorous stomach contents were obtained, which did not show blood, either chemically or microscopically; total acidity 50, no free HCl. Thereafter blood was found in the stools continuously until July 29. Under the citrate of iron treatment the hemoglobin rose steadily and reached practically the normal by August 12, 1914, when the child was again discharged in an excellent condition.

The patient was readmitted February 15, 1915. Since her previous discharge the condition had remained good up to seven weeks before admission, when the mother noticed an increasing pallor, ascribed to the presence of tarry stools; but there was no vomiting. On the day preceding admission, at 9 P.M., the last previous meal having been taken at 2 P.M., she vomited a glassful of dark coagulated blood, and again at 11 P.M. half a glassful of bright red blood.

The physical examination revealed, in addition to the previous findings and the anemia a spleen, which reached 1.5 cm. below the free border of the ribs. On the day of admission the vomiting of blood continued, and there were also several tarry stools. Examination of the blood showed the following:

Hemoglobin	28	per cent.
Red blood cells	1,600,000	
Leukocytes	20,000	
Polynuclears	89	per cent.
Small lymphocytes	10	"
Large lymphocytes	1	"
Moderate poikilocytosis		

On this day the child was transfused by Dr. Lewisohn by the citrate method. Ten hours after transfusion the hemoglobin was 33 per cent.

February 16th, profuse hematemesis.
February 17th, and 18th, several tarry stools.

Hemoglobin	30	per cent.
Red blood cells	800,000	
Leukocytes	26,000	
Polynuclears	90	per cent.
Large lymphocytes	10	"
February 20th. Hemoglobin	25	"

February 21. I was requested to see the patient, and advised an exploratory operation, the most probable diagnosis being that of an ulcer in the vicinity of the pylorus; the operation to be preceded by another transfusion, in order to raise the hemoglobin to safe limits.

February 22. Hemoglobin only 14 per cent.; 450 c.c. of blood were transfused by Dr. Lewisohn, which raised the hemoglobin to

37 per cent. Immediate operation. Median epigastric incision four inches long. Considerable serous fluid in the free peritoneal cavity. A very thorough examination of the stomach and duodenum failed to reveal even a suspicion of an ulceration. The liver appeared to be normal. The spleen was slightly enlarged.

After operation there was absolutely no change in the condition of the patient, as may be seen by the following notes:

February 23. Hemoglobin, 50 per cent.; bleeding time, nine minutes.

February 26. Hemoglobin, 45 per cent.; bleeding time, eight minutes.

February 28. Hemoglobin, 28 per cent.; coagulation time, six minutes; bleeding time, eight minutes.

March 2. Hemoglobin, 25 per cent.; coagulation time, six minutes; bleeding time nine minutes.

March 3. Hemoglobin 17 per cent.; coagulation time, five minutes; bleeding time, eight minutes. On this day the patient was seen by Dr. Koplik, who, in view of the futility of all therapy, and because of the continuation of the bleeding, advised another transfusion. This was done on March 4 by the Unger method, raising the hemoglobin to 50 per cent.

March 5. Hemoglobin, 46 per cent.; coagulation time, seven minutes; bleeding time, fourteen minutes.

March 6. Hemoglobin, 50 per cent.; coagulation time, five minutes; bleeding time, nine minutes.

March 7. Hemoglobin, 43 per cent.

March 8. Hemoglobin, 38 per cent.

Thereafter the hemoglobin in spite of occasional tarry stools remained stationary. The wound being perfectly healed, the child was retransferred to the service of Dr. Koplik; and I wish to acknowledge my indebtedness to him for both the pre-operative and final notes of the case.

April 2. Patient vomited four ounces of clotted and fluid blood. Melena.

April 3. Melena.

April 5. Hemoglobin, 16 per cent.

April 13. Patient vomited about eight ounces of clotted and fluid blood. On this day examination of the blood revealed the following values:

Hemoglobin	15	per cent.
Red blood cells	1,616,000	
Leukocytes	8,800	
Polynuclears	44	“
Small lymphocytes	36	“
Large lymphocytes	10	“
Transitionals	1	“
Myelocytes	5	“
Basophiles	1	“
Myeloblasts	2	“
Normoblasts	4	per 100 leukocytes
Megaloblasts	1	“ “

Marked pallor of the red cells; moderate poikilocytosis and anisocytosis; polychromatophylia.

April 15. A transfusion by Dr. Lewisohn of 380 c.c. of citrated blood raised the hemoglobin from 13 to 30 per cent.

After this final transfusion for some unexplained reason the vomiting and melena ceased; the hemoglobin began to rise; patient was soon able to leave the bed, and was finally discharged in very good condition May 3, 1915.

These are the histories of the four personally observed cases; all of them seen within a period of less than one month and three within a period of two days. I confess to considerable chagrin and disappointment, as in all of them I had made, or at least concurred in, the diagnosis of a bleeding ulcer of the stomach or duodenum with a degree of confidence which bordered upon positiveness.

Review of the Literature. In the older medical literature the statement is frequently made that bleeding from the stomach may occur by diapedesis; but with the advent of careful pathological and microscopic examinations the theory of bleeding by diapedesis has been found to be untenable. The generally accepted view now is that all bleeding from the stomach, particularly that of larger quantities, must be the result of a defect in the mucosa. Such a defect was, however, not determinable by the conventional methods of examining the stomach *in vivo*, for I assume that it would have been unjustifiable on my part, in view of the poor condition of my patients, to make a wide opening into the stomach, to permit of thorough interior exploration.

A study of my personally observed gastric material and a critical review of the literature upon the subject lead me to the conclusion that all defects of the gastric mucosa other than neoplastic may be grouped under the following three forms:

1. The "*mucous erosions*,"[1] so called, accredited to Einhorn.
2. The "*exulceratio simplex*,"[1] so called, accredited to Dieulafoy.
3. The "*true gastric ulcer*,"[1] of Cruveilhier.

1. "*Mucous Erosions*." I have had very little experience with this group, certainly not sufficient to warrant me to pass an opinion upon the subject, but a study of Einhorn's publications,[2 3 4 5] as well as of similar articles by Pariser,[6] Mintz,[7] Hageman and Jones,[8 9 10]

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[1] It is regrettable that these terms are used so indiscriminately and interchangeably by different authors. I believe that the nomenclature, as I use it, is correct.

[2] Berl. klin. Wchnschr., 1895, p. 435.

[3] Jour. Am. Med. Assn., 1870, p. 1079.

[4] New York Med. Jour., 1908, p. 777.

[5] Diseases of the Stomach, New York, William Wood & Co.

[6] Pariser, Berl. klin. Wchnschr., 1900, p. 954.

[7] Ztschr. f. klin. Med., 1902, p. 115.

[8] Inaug. Dissert., Freiburg, 1909.

[9] Jour. Am. Med. Assn., October 14, 1911, p. 1265.

[10] Northwest Med., February, 1912.

will very quickly show that none of my cases could very well belong to this group.

The symptomatology and physical signs of this malady (if at all a clinical entity, which is doubted by some observers) are not at all well marked; the chief characteristics of the ailment are the presence of small bits of mucous membrane in the lavage water and the absence of hematemesis. The presence of very profuse gastric hemorrhages in all of my cases is sufficient to exclude them from this group.

2. "*True Gastric Ulcers.*" I have also excluded my cases from the third group, or the group of true ulcers. This exclusion must, of course, be accepted with a certain amount of mental reservation. I justify my procedure upon a fairly extensive operative experience with ulcers of the stomach and duodenum, which has led me to the belief that their recognition is a comparatively easy matter. It should also be taken into consideration that my professional pride would naturally have acted as an incentive to the most painstaking examination in these four important cases, in order that the preoperative diagnosis of ulcer might be upheld. I must assume, therefore, that the gross ulceration, or true gastric ulcer, I so confidently expected to find, did not exist.

3. There remains therefore only group two, or "*exulceratio simplex*" of Dieulafoy, so called. I am confident that if my cases are studied from the point of view of diagnosis it will be found to correspond to all the requirements attributed to this group.

While Dieulafoy has been antedated by a number of writers, notably Chiari[11] and Murchison,[12] in the report of cases of massive or even fatal gastric hemorrhages, in which the autopsy revealed either a trivial lesion or even an entire absence of any lesion, it was undoubtedly his masterly and vivid description, and more particularly the recovery of his second case, after an operation, deliberately undertaken to check the hemorrhage, which has awakened the interest of the medical profession to the malady under discussion; in fact, we frequently find it spoken of as "Dieulafoy's ulceration." For the sake of historical correctness I may be pardoned for abstracting briefly Dieulafoy's two cases.

Dieulafoy[13] reports the following cases:

CASE I.—Male, aged twenty-seven years, admitted to the hospital November 13, 1896, for hematemesis, which began without any premonitory symptoms at noon of the day of admission. Patient states that he lost two or three liters of blood; although Dieulafoy doubts the correctness of this statement, he is certain that the loss of blood must have been very great. He was treated by absolute rest, ice-bag to the abdomen, and ergotin injections. The hematemesis recurred that night, and was followed by melena. The total amount of blood lost was estimated at four liters. Patient was in a desperate condition. Dieulafoy considered the advisability of surgical interference, but abandoned it. An intravenous saline infusion was followed by temporary improvement only, as patient died within less than thirty hours from the onset of the gastric hemorrhage.

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[11] Prag. med. Wchnschr., 1882, p. 489.

[12] Tr. Path. Soc., London, 1870, xxi, 162.

[13] Bull. de l'Acad. de méd., Paris, 1898, p. 49.

The autopsy revealed the following points of interest. On incising the stomach half a liter of blood was found, but to everybody's surprise, at first, no ulcer was seen. Carefully washing away the blood, there was discovered 2 cm. distal to the cardia, a very superficial "exulceration" of the size of a five franc piece. The borders of this exulceration were not indurated, nor elevated; upon the base, which was grayish white and soft, there were to be seen two or three small ecchymotic spots, and two craterlike erosions. In one of these there was seen a small open arteriole, into which it was possible to introduce the point of a pin.

The subsequent histological examination showed that the defect in the stomach involved only the mucosa and submucosa; and even the latter not throughout the entire defect. All the other coats were normal. In the bottom of one of these crater-like erosions there was an open arteriole, which was the source of the fatal hemorrhage. The coats of this arteriole, a branch of the coronary artery of the stomach, showed neither a periarteritis nor an endarteritis. The veins in the vicinity were dilated and thrombosed, and explained the ecchymotic appearance above mentioned.

When Diuelafoy saw the specimen he regretted extremely his decision not to call for surgical aid, and fully made up his mind to act differently on a future occasion. This occasion presented itself in

Case II.—On October 18, 1897, there was admitted to his hospital service a male, aged twenty-two years, who gave the following history. On the evening of October 7, after having eaten a hearty meal, he became nauseated and vomited a quantity of blood, which he estimated at one or two liters. He was very much weakened thereby, but passed a comfortable night. On the following day he again vomited large amounts of both fluid and clotted blood. Prior to this attack patient never had any gastric symptoms.

When admitted to the hospital he presented all the symptoms of a profound anemia. From his appearance, Dieulafoy estimated that he must have lost three or four liters of blood.

From the history and symptoms, and by a process of exclusion, Dieulafoy arrived at the conclusion that this patient was suffering from the same kind of "exulceration" as Case I. While he knew from his previous experience that if something energetic were not undertaken he would probably lose the patient, Dieulafoy hesitated to advise so radical a procedure, in the state of gastric surgery, as it existed at the time; he therefore temporized and treated the patient expectantly.

On October 16 patient vomited exactly 1 liter of fluid and clotted blood. Extreme pallor, pulse imperceptible. Being certain that the patient would die upon the accessoin of another hemorrhage, he referred the patient to a surgeon, M. Cazin.

Cazin operated only upon the insistence of Dieulafoy, as the outlook otherwise was hopeless. On exposing the stomach nothing suspicious was found, neither to sight nor to touch. The stomach was therefore incised and the interior everted and explored. At first nothing was found, but on cleaning away the stomach contents he was rewarded by seeing a tiny "exulceration" on the posterior wall of the stomach near the cardia, about the size of a 50-centime piece. On gentle sponging, bleeding began again; however, it was not an ordinary gastric ulcer, with indurated and elevated borders, but merely an exulcerated surface, comparable to that described in Case I.

The ulcer was sutured from within the stomach, and the operation finished in the uusal manner. Patient recovered.

In addition to these two personally observed cases Dieulafoy was able to find three other similar cases in the practice of his colleagues (Michaux, Gilbert (2)); also one case which is published by Luys[14] and by Lepine and Bret.[15]

Dieulafoy's observations apparently did not fall on very fertile ground except in England, because it is in England only that we find similar cases reported with any degree of frequency. Cases of a similar nature, however, to the number of less than fifty have been reported in England by Steven, Mackenzie, Hood, Armstrong (Montreal), Mansell Moullin, Hale White, Dawson, Harrington, Mayo Robson, Symonds, Moynihan, Eve, Guilford and others. Very few cases have been reported on the Continent, Banti, Monprofit, Harttung, Hampeln, Berger, etc. It is somewhat difficult to estimate the frequency of the malady in the United States, judging merely from the literature; this is due to the fact that almost all authors, writing upon this or allied subjects, speak of these exulcerations with such a degree of familiarity as to lead one to believe that they are matters of frequent personal experience; and yet when we come to look for actual and bona fide observations we find but very few. An exception is Deaver,[16] who in a paper entitled "Gastric Hemorrhages," distinctly states that he has operated in six cases belonging to this group. It is to be regretted, however, that none of these cases are reported in detail. It is very probable that some of the cases mentioned by W. Gilman Thompson[17] belong to this group; and it is also possible that one or another of the ten cases of operation for gastric hemorrhage reported by Lund, Joslin and

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[14] Bull. de la Soc. anat., 1896, p. 660.

[15] Arch. de Méd. expér. et d'anat. path., 1893, p. 254.

[16] Surg., Gynec. and Obst., xviii, 294.

[17] Am. Jour. Med. Sc., September, 1905, p. 357.

Murphy[18] may be of a similar nature, because in some of these a fairly adequate search during the operation failed to reveal any bleeding point or ulcer. Cases have also been reported by Abbe,[19] Andrews and Eisendrath,[20] Rodman[21] and others.

I have permitted myself considerable latitude in admitting cases into this group, but there are some, reported under this heading, which, for various reasons, I have found necessary to exclude. I mention, for instance, the cases reported by Jones,[22] in which at autopsy the stomach and upper bowel were found to be free from ulcer, erosions, scars, eroded vessels; in fact, everything that might have led to hemorrhages. Jones claims that the bleeding had taken place from a gastric erosion and that sufficient time had elapsed for healing to take place.

I shall also exclude the case observed by Pilliet and Deny.[23] Fatal hematemesis in an insane male person, aged fifty-eight years. At autopsy a number of minute "hemorrhagic erosions" were found, both in the stomach and duodenum. My reasons for excluding this case are that there was a history of the swallowing of a number of metallic foreign bodies which obviously may have produced the lesion.

An exceedingly accurately observed case is that of Hirsch.[24] I am, however, of the opinion that it does not properly belong into this group, because a scar was found in the stomach, from the center of which the hemorrhage issued; and I believe that Dieulafoy's ulcerations are particularly characterized by the absence of scars. The patient was a female, aged nineteen years. There was a history of chlorosis and also of gastric disturbances with hematemesis. After a railway accident, however, without any direct trauma to the abdomen, there was a very profuse gastric hemorrhage. Autopsy at first showed nothing; only after repeated careful examinations there was discovered a white scar the size of a lentil, having in its center a pin-head sized perforation leading into an open vessel.

SYMPTOMATOLOGY AND PHYSICAL SIGNS. A typical example of "exulceratio simplex" Dieulafoy can be said to have only one well-marked symptom, namely, profuse hematemesis. This is such a characteristic symptom that we may divide the entire symptomatology into two parts, (1) before, and (2) after the occurrence of the hematemesis.

Before the occurrence of the hemorrhage the history and physical signs are to all intents and purposes negligible. We find in a majority of instances that the afflicted individuals have no complaints referable to the stomach. The appetite and digestion are fair, and the general health is so good that there does not exist at any time suspicion of impending danger. Suddenly and without any warning the patient vomits blood. It is rather characteristic that the first vomiting is so profuse that the patient shows systemic signs of bleeding. There are cases recorded in which even the first hemorrhage was fatal.

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[18] Boston Med. and Surg. Jour., August 4, 1904.

[19] New York Med. Jour., May, 1891.

[20] Ann. Surg., 1899, xxx, 393.

[21] Philadelphia Med. Jour., June 9, 1900, p. 1302.

[22] Northwest Med., February, 1912.

[23] Gaz. méd. de Paris, 1893, p. 401.

[24] Berl. klin. Wchnschr., 1896, p. 847.

The physical signs before hemorrhage are not known, for obvious reasons; but in view of the absence of symptoms before hemorrhage it is safe to assume that the physical signs must also be negative.

After hemorrhage has taken place the symptoms and physical signs which govern the disease are merely those of a profound anemia. Examination of the stomach reveals nothing noteworthy. In the few cases in which the gastric contents were examined, nothing characteristic has been found. In some cases a marked hyperacidity, in some normal values, and in others even a hypoacidity has been found.

The disease affects most frequently females in the early twenties; but males in the later years of life, and even children, are not immune.

Hale White,[25] under the title of gastrostaxis, also called attention to gastric hemorrhages, which are not caused by true ulcers, and in many of which the true source of the bleeding has remained undiscovered. If his case reports are carefully examined it is manifest, that he has been describing nothing more nor less than Dieulafoy's ulcer. In a few of the case-reports the source of the bleeding was not discovered, but this was probably due to hasty, or at least insufficient examination.

Pathologically these cases differ from the gastric erosions of Einhorn, in the fact that while in the latter the defect in the gastric mucosa is so superficial as not to involve even the entire thickness of the mucosa (indeed, no postmortem examinations have ever been made, to my knowledge), the defect in Dieulafoy's ulcerations extends at one point, at least, throughout the entire thickness of the mucosa, involves the submucosa, and has eroded a vessel of appreciable size. It is in this characteristic only that we can account for the presence of notable hemorrhages in the latter and their absence in the former. Neither one of these ulcerations is accompanied by any palpable induration, infiltration, or thickening. When eventually such a lesion heals it does so without any recognizable cicatrix formation, and therefore never causes any deformities in the shape of the stomach. Finally, in true ulceration of the stomach, the defect invades more of the coats of the stomach, even to and through the serosa. There is considerable infiltration of massive induration, which renders their recognition by the examining finger very easy, and when such ulcerations heal they do so by the formation of a true cicatrix, resulting in appreciable deformity of the stomach.

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[25] Lancet, November 3, 1906.

The question of the relationship between the simple exulceration of Dieulafoy and the true gastric ulcer of Cruveilhier has not yet been definitely decided. Some observers take a definite affirmative stand, notably Gerhard;[26] others, as, for instance, Langerhans,[27] deny any relationship between the two, or admit it only as a very exceptional occurrence.

CHRONIC INTESTINAL STASIS.[1]

By G. R. Satterlee, M.D.,

ATTENDING PHYSICIAN TO FORDHAM HOSPITAL, CHIEF OF CLINIC FOR GASTRO-ENTEROLOGICAL DISEASES, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK.

(From the Gastro-enterological Department of the University and Bellevue Hospital Medical College.)

Is it not necessary clearly to define the terms "stasis," "constipation," and "intestinal toxemia?" For they have been used loosely and interchangeably, much to the confusion of students of the subject. The term "stasis," from its derivation, may be an excellent one to denote areas of local stagnation in the bowel, and if thus limited it would come into general usage. Now, however, there is a tendency to utilize the term to denote the systemic condition, more properly, as it seems to us, described as intestinal toxemia. For this reason, and to avoid confusion, the author has chosen to discontinue its use, confining himself to the generic term toxemia and to the old term constipation as denoting areas of local delay in the bowel.

Chronic intestinal toxemia[2] is a diffuse intoxication of unknown origin, the result of aberrant biochemical conditions, usually, but by no means always, bearing a measurable ratio to the delay in the onward passage of the intestinal contents, as visualized by the roentgen-ray.

In considering this complex of toxemia, therefore, it is convenient, as shown in the tables, to classify them for analysis according to the areas of bowel which are locally effected. This also affords at once a working basis for rational treatment, being merely an application of the direct or objective method to the alimentary canal. This seems logical and timely, for gastro-enterologists should not linger behind the genito-urinary or other progressive specialists who have long since given up the old subjective methods of diagnosis.

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[26] Virchows Arch., 1892, cxxvii, 85. [27] Ibid., 1891, cxxiv, 373.

[1] Read before the Jefferson Medical College Clinical Society, Philadelphia, January 28, 1916.

[2] G. R. Satterlee, Chronic Intestinal Stasis, New York Med. Jour, June 12, 1915.

Regarding the etiology of toxemia very little is known, but it has been supposed that constipation was the usual exciting cause. Whether the origin of the toxemia is traceable to bacterial causes or to disturbance in the internal secretions of the gut itself is unproved, but of the two the bacterial hypothesis has rather more support than the biochemical, from our therapeutic results. Nevertheless, though many mild cases respond to a protein-free diet, graver ones usually will not, and these in turn may or may not react favorably to autogenous colonic vaccines. One thing is certain from the study of this series, namely, that congenital or acquired deformity of the gut is a strong predisposing factor.

Regarding pathology, our studies at the present are incomplete, but we have one fixed conclusion, namely, that observations to be of any value at all must be made upon the fresh postoperative tissues rather than upon dead-house material, the latter having led many observers into the gravest kind of errors on account of the rapidity of postmortem changes. It is encouraging to note that all of the developmental reconstruction cases have shown extensive as well as widely differing gross and microscopic lesions. Furthermore, some of the cases showed fresh local peritonitis and enlarged mesenteric glands, from which colon bacilli in pure culture were isolated.

Symptoms remain the dominant factor in establishing a diagnosis. And are they not familiar to us all? Rightly divided into mental, physical, and nervous, simple and seemingly isolated as these appear to be, is it not evident with our recent knowledge that we have failed properly to understand their significance and to interpret their meaning? What multitudes of sufferers from neuralgias, myalgias, neuritides, hemicranias, neurasthenias, amauroses, etc., are being maltreated for the symptom rather than for the cause. And yet how little we know regarding the greater problems of the relation of this subtle yet powerful toxemia to the more serious and better defined lesions of cardiovascular, central nervous, and genito-urinary systems, which some of the more advanced observers consider to be reflections of this fundamental bowel perversion. Comparative pathology has not advanced far enough to settle the problem; indeed, it cannot well do so, unaided by biochemistry, but the relative immunity of the quadrupeds from human lesion is significant. In considering this, does it not seem rather odd that the sigmoid, which not infrequently causes us much trouble, is absent in the quadrupeds, occurring only in the apes and in man; an example perhaps of the overspecialization of an organ frequently referred to by Lynch and Draper.

At present, however, we must be content to consider the first mentioned symptoms rather than the better recognized entities in the relation of cause and effect to intestinal toxemia and leave to the future an explanation of its bearing upon such intricate conditions as blood-pressure and sclerosis.

In general, it cannot be too strongly emphasized that every patient presenting any of the simple symptoms above mentioned should be looked upon as essentially autotoxic until proved to be otherwise.

Classification of these cases of intestinal toxemia, according to symptomatology, is too indefinite, so I have adopted one according to the location or locations of the lesion. Neoplasms and unusual obstructions omitted, the following classification is submitted:

(*a*) Gastric delay, due to gastric atony, water-trap stomach, and reflex causes.

(*b*) Duodenojejunal obstructions, so frequently looked upon as evidence of intestinal toxemia and believed by Lane and Bloodgood to be mechanical.

(*c*) Ileocecal obstruction and non-obstructive ileal constipation.

(*d*) Chronic appendicitis.

(*e*) Cecal dilatation and constipation.

(*f*) Atonic constipation of the colon, especially of the transverse portion. (Under here may also be grouped the dubious so-called spastic constipation.)

(*g*) Sigmoid constipation.

(*h*) Lesions of the rectal outlet.

(*i*) Combinations of these forms.

We do not as yet seem to have reached the point where there is uniformity in radiographic work, so the character and amount of the bismuth and barium meals used in these cases are as follows: For the bismuth meal, 96 grams of bismuth subcarbonate in 960 grams of fermented milk; and for the barium meal, 150 grams of barium sulphate, 32 grams of cane sugar, 32 grams of flour, and 32 grams of cocoa were used. The barium meal is more palatable and is of the same value in radiography. In all cases a bismuth or barium colon injection is given after the colon is emptied of the first meal by enema, radiographs taken immediately and twenty-fours after for "residues." Every other consideration fades before the all-important problem of diagnosis. It is well to have clearly in mind the relative value of the data upon which this is to be based. First is the subjective history; second, the roentgen-ray; third the objective history; fourth, the laboratory findings.

The autotoxic patient's chief complaint, as shown by the tabulated study of 136 cases, is extremely variable. In fact, its variability and its apparent complete separation from the intestinal canal are often its chief characteristic.

Constipation as a primary or secondary complaint appears in 114 cases, or 84 per cent.; diarrhea, in 39, or 30 per cent., of which number 30 gave a history of both diarrhea and constipation. In

5, or 3.5 per cent., the history was unreliable, and in 8, or 6 per cent., the bowel movements were normal. Colica mucosa occurred in 59, or 43 per cent. Flatus to a marked degree in 104, or 76 per cent. Loss of weight occurred in 80, or 60 per cent. Mental symptoms, varying from simple inefficiencies to melancholias and epilepsies, deliria and stupors, occurred in 54, or 40 per cent. Nerve symptoms, neuralgias, etc., occurred in 88, or 65 per cent.

Motility is the cardinal point gained from the roentgen-ray. The patient's intestine may be ptosed to any degree without causing any symptoms. Although enteroptosis was absent in only 30, or 22 per cent., it was probably a strong predisposing factor in their illness, as shown by therapeusis.

Gastric constipation is determined by remnants of the bismuth or barium meal six hours after ingestion. Delay on this basis occurred in 54 cases, or 40 per cent. In only one was organic obstruction apparent.

Ileal constipation, shown by retardation in the terminal ileum, was present in 3; ileal obstruction by Lane's kink was relieved by operation in 1.

Cecal constipation, or the term "residual cecum," is determined by remnants of bismuth or barium in the cecum and oral part of the ascending colon, forty-eight hours after ingestion. It was present in 58, or 42 per cent., and was apparently responsible for much of the symptomatology in these patients.

Colonic delay was determined by the same method. A duration of between forty-eight and seventy-two hours in 13, or 9.5 per cent.; of seventy-two hours or over in 75 or over 50 per cent. of the cases; in 15, or 11 per cent., the colon was emptied in twenty-four hours.

Sigmoid constipation, or the term "residual sigmoid," was considered when the sigmoid flexure failed to empty at the end of three days. It was noted in 47, or 34.5 per cent., and associated with "residual cecum" in 22, or 16 per cent., and was uncomplicated by constipation in other parts of the gastro-enteric tract in 8 cases, or 6 per cent.

The association of gastric, cecal, and sigmoid constipation was very instructive. Gastric constipation, uncomplicated and due to elongated stomachs with a long pyloric arm (12 c.m. or over), the so-called water-trap stomach, was present in 7, or 5 per cent.; water-trap stomach, with residue and intestinal adhesions, in 3; water-trap stomach with residue and obstruction in cecum, 2; water-trap stomach with residue and cecal constipation, 7, or 5 per cent.; water-trap stomach with residue and sigmoid constipation, 2; "residual stomach" with no apparent anatomical abnormality and sigmoid constipation, 2.

Gastric, cecal, and sigmoid constipation combined (normal types of stomach) occurred in 6 cases; the same due to neuroses of known etiology in 2 cases; gastric constipation with chronic appendicitis (proved at operation) in 5 or 3.7 per cent.; gastric constipation and ileocecal obstruction, 1; gastric constipation with perirectal adhesions, 2 cases.

Of the entire series, 33 or 25 per cent. had had the appendix previously removed without lasting benefit to the chronic condition.

Our observations upon the colonic vaccines have been significant both in differential diagnosis and in therapy. Of course, the subject is undeveloped and not one permitting of dogmatic deductions. Whatever the final decision, any form of therapy which in some cases achieves great benefit to the sick and can do no harm, and which at the same time stimulates research and throws some light on questions of etiology, is a good therapy.

The vaccine is prepared in the usual way from the prevailing type of colon bacillus, isolated from the patient's feces. The dosage is of very great importance, and injections should not be given when the bowel is loaded, else an unnecessarily severe reaction is apt to result. This in itself is an interesting and perhaps significant fact. The initial dose has been from 25,000,000 to 50,000,000, continued at intervals from four to seven days, and the maximum dose 300,000,000 bacilli.

In typical cases of chronic intestinal toxemia, usually a reaction is experienced within twenty-four hours. This consists of a small, red, painful, and slightly indurated area, the size of a dime or nickel, slight headache, giddiness, or nausea, increase in the neuralgic or myalgic pains, occasionally increased peristalsis, followed by marked relief of symptoms in forty-eight hours. So far no cases in which a typical severe reaction has occurred have been free from what is considered chronic intestinal toxemia, showing the diagnostic value of the procedure. A few examples will suffice to show results. In a patient with marked enteroptosis and a chronic intestinal obstruction and attacks of vomiting of duodenal contents, vaccines alone would check the vomiting after the ordinary well-known methods had been tried. Reactions were severe, but this treatment relieved on various occasions, and the patient is still alive, declining operation.

At the present time two other patients needing but constantly refusing operation for intestinal obstruction have been kept on their feet, one for three months, the other for a year. The first patient has probably an adhesive appendicitis and is improving; the second has just been operated upon, and strong bands of adhesions across the ascending colon and adhesions of a displaced uterus to the rectum found. She had numerous physicians and different kinds of treatment for years, most of the physicians advising operation. No treatment except the vaccine gave any real relief, and she had been dependent upon the vaccine for nine months prior to operation. Several other cases of a similar type and results could be quoted if time would permit. One of the most striking results, however, was in the case of a patient who had intestinal toxemia for years, with profound depression amounting to insanity for two years. The urine was saturated with indican and she was mentally incompetent. The colon was kinked and diseased. Developmental reconstruction of the colon was done by Lynch and Draper, but the mental condition became worse with delirium and coma, severe albuminuria with all kinds of casts, and for a week she was expected to die hourly. Autogenous colon vaccines were given followed by very severe reactions, increased delirium, restlessness, and the patient had to be restrained to the bed. These reactions lasted for from eight to twelve hours, followed by a period of calm and general improvement and a diminution of the indican and albumin and casts. Vaccines were administered every four days for a month and a half, when they were discontinued, the patient leaving the hospital weak but in good mental condition. It was then for the first time that I obtained an intelligent connected history from her. Two years after the operation she is in good physical and mental condition. I quote from the nurse's notes:

"November 4, 1914. Second dose of vaccine, 75,000,000. Slight rise of temperature, marked rapidity of pulse, extreme restlessness and slight delirium, lasting twelve hours."

Doctor's notes on November 16, the beginning of the sixth week after the operation.

"Marked improvement in the general condition and spirit; noises in the ears still present; crash of paper causes agony; can read the dial on the watch for the first time today."

Nurse's note on November 20, after the sixth dose of the vaccine.

"Difficult breathing, immediate weakening of the pulse. One hour after, pulse hardly perceptible, responded to stimulation slightly; weak and exhausted condition; lasted twelve hours."

Urinalysis: Albumin diminished, indican still in large quantity.

December 2. Ninth dose of the vaccine, 100,000,000, reaction very slight, general condition improved. Urine, no albumin, moderate amount of indican. Apparently the colon vaccine saved her life.

The exact mode of action of the colon vaccine is by no means clear. When the author began to use the autogenous product four years ago it was with the idea that at least some of these cases of intestinal toxemia were bacterial in origin and that some sort of immunity against the colon organism could be established by injecting their toxins. Three years ago Adami[3] spoke of "subinfection in auto-intoxication," and that the intoxication could be caused by bacterial ectotoxins. He says that the members of the B. coli group produce no recognizable ectotoxins; the same also is true of another important group, the streptococci. If this be true the intoxication could be only through bacteriolysis, through breaking down and liberation of their split products.

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[3] Chronic Intestinal Stasis, Auto-intoxication and Subinfection, Colorado Med. Jour., Denver, 1914, xi, 34.

It is the general consensus that vaccines are useful for the cure of local infections, but they may also be of use in some general instances. If it is true that intestinal toxemia is due in some cases to the end products of colon infection and that the infection is localized to the intestinal tract or its immediate neighborhood, immunization by means of vaccines would not be an irrational method, just as their usefulness has been recognized by some in colon infections in the genito-urinary tract or elsewhere.

The local infection by the colon bacillus in the portion of the large intestine removed at operation has been demonstrated and the bacilli recovered from some of the mesenteric lymph nodes, as already stated.

Bassler,[4] in 1910, published results of treatment of chronic intestinal putrefactions by means of rectal instillations of autogenous bacteria and strains of human Bacillus coli communis. In the literature I have been unable to find mention of treatment of this condition by subcutaneous or intravenous administration of the autogenous product.

CLINICAL HISTORIES OF THE TEN TABULATED CASES.

Case I (on chart).—W. W. B., male, aged thirty-three years, married. Whole family is nervous, and they have "indigestion." Nothing noteworthy until seven years ago, when he had "ptomaine poisoning." Since then has been progressively constipated, with attacks of vomiting and severe eructations. In the past three years the attacks have been more frequent and more severe, lasting two weeks, with shorter intervals between attacks. Vomits food and bile, and has long strings of mucus in the stools. Appendectomy two years ago. Has lost 40 pounds, and is unable to work. Obstipation severe. Marked emaciation; vomits and eructates large quantities of gas when touched. Blood-pressure, systolic, 170; diastolic, 120. Arteriosclerosis marked. Diagnosed as chronic interstitial nephritis. Our diagnosis, intermittent obstruction in colon. Radiographs showed water-trap stomach, $3\frac{3}{4}$ inch ptosis, delay in ileum, marked coloptosis and delay in transverse colon and sigmoid.

Operation. Loose typhon and volvulus formation. Reconstruction of colon by Drs. Lynch and Draper. Slow recovery aided by colon vaccines, but well and at work in two years; blood-pressure returned to normal. Is naturally careless.

Case II.—C. B. Insanity, with marked intestinal toxemia. Described previously; reconstruction of colon; toxemia cleared up by colon vaccines.

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[4] Bassler, A., Med. Record, September 24, 1910.

Case III.—M. D., female, aged twenty-seven years, married. Her sister has a similar gastro-intestinal condition. Eight years, following the birth of the first child, severe constipation, occasionally colica mucosa, and diarrhea. Headaches, pain in eyes, vertigo, occasionally vomiting and hemorrhoids. Flatulence marked, with difficulty in passing gas per rectum. Dragging sensation in the lower abdomen and pain in the right lower quadrant. Medical treatment for gastro-intestinal condition for four years and ventral suspension of uterus one year ago. No improvement. Lost 12 pounds. Examination one year ago showed toxic appearance, marked enteroptosis. Radiographs showed enteroptosis and residual cecum.

Operation. Reconstruction of the colon for a loose diseased organ. After treatment: abdominal support and autogenous colon vaccines. Complete recovery within one year.

Case IV.—R. B. E., female, thirty-three years. As a child undeveloped and "poor assimilation." Always constipated with attacks of colica mucosa. Numerous operations; gangrenous appendicitis, cystic ovary, displacement of uterus and adhesions, torn perineum and sepsis following childbirth. Also for gall-stone and adhesion of gall-bladder to colon.

Neurasthenic, neurotic, and melancholic to an extreme degree. Christian Science and hypnotism of no help.

Radiographs showed enteroptosis, marked residue in cecum and sigmoid, which was enormous. Reconstruction of the colon, with slow recovery, aided by colonic vaccines. Secondary operation for obstruction at operation site followed by ultimate recovery.

Case V.—C., female, aged thirty-eight years, married. Family history of migraine. Possibility of luetic infection, with one positive Wassermann reaction. Three doses of salvarsan and mercurials; temporary relief of symptoms and negative serum and spinal fluid reactions. Series of severe headaches, vomiting, constipation, and hemorrhoids. Flatulence, but no gas, passed per rectum. Symptoms began after birth of child fifteen years previous. In bed the greater part of the time. Lost 40 pounds. Improved for a year and symptoms became worse with severe pain in region of gall-bladder. Radiographs showed "residue" in cecum and three days bismuth in colon.

Laparotomy. Gall-bladder normal with small adhesion to colon. Cecum and ascending colon enormously dilated; duodenum also dilated; practically a volvulus formation. Reconstruction of the colon. Recovery and patient passed gas by rectum "for the first time in twelve years." Return of headaches one year later with evidences of cerebrospinal fluid pressure but these disappeared and patient is well three years after operation; gained 50 pounds.

Case VI.—H. R., male, aged twenty-five years, married. For eight years had constipation, frequent attacks of pain in right iliac region and nausea after eating. Extreme tenderness in right lower quadrant, palpable and crepitating cecum. Diagnosis of appendicitis and residual cecum and sigmoid. Stomach was normal; no enteroptosis.

Operation. Cecum and ascending colon chronically inflamed and covered with fibrinous flakes; long appendix, inner third bound down by firm adhesions; enlarged mesenteric glands. Partial reconstruction of colon and hemorrhoidectomy. Recovery, with normal bowels, three months after.

Case VII.—W. L. R., male, aged thirty-five years; married. Father died with a hemorrhage from the stomach; mother with carcinoma uteri. History dated from five years ago, following severe mental strain, and symptoms have consisted chiefly of extreme nervousness and "obsessions." He was unable to enter a strange place to eat or to go into a room where strangers were or to leave the same. Sensations of strangulation and faintness, and practically unable to conduct his own business. Markedly enteroptotic, gurgling, and crepitation over cecum. Radiographs showed residual water-trap stomach and cecal constipation. Feces showed excessive fermentation and putrefaction. Two years' treatment by a competent neurologist, with no particular attention to the gastro-intestinal tract, had given no improvement. Medical treatment for intestinal toxemia, with abdominal support and diet and colon vaccines, resulted in marked improvement in less than six months.

Case VIII.—J. F. S., female, aged forty-five years; married. Daughter has a very similar condition of the gastro-intestinal tract. For years patient had had severe constipation, progressive neurasthenia, flatulence, loss of weight, abdominal discomfort (feeling of "drag"), headaches, and neuralgias. For past year vomiting, with purging and chills. Markedly enteroptotic. Radiographs showed water-trap stomach with five-inch drop and large residue at six hours. Cecal constipation and sharp angulation at hepatic flexure. Long sigmoid.

Operation. Coffey suspension of colon with Beyea shortening of the gastrohepatic ligament. Recovery gradual, aided by abdominal support, antitoxic diet, and colon vaccines. Three years after was well, except for slight intestinal toxemia, and gained 20 pounds.

Case IX.—B. R., female, aged forty years; single. No family history of intestinal trouble. A year and a half ago her bowels began to be loose, with pains in the stomach and in the right inguinal region. Since then diarrhea, alternating with constipation, and for the last six months stools were hard and ball-like, covered with mucus. Lost 30 pounds. Markedly enteroptotic. Gurgling and crepitation over cecum and tenderness over whole colon. Water-trap stomach, with large residue at six hours. Treatment for the enteroptosis and intestinal toxemia improved patient much at first, but on account of the continual pain and tenderness in the appendicular region the diagnosis of chronic appendicitis was made and operation advised. This was finally done by some other physician, but the symptoms have not cleared up, probably because of lack of proper medical after-treatment.

Case X.—R. C. D., female, aged thirty-four years; married. Eight months' baby; weak and did not walk until three years. Fell on the ice when fifteen and had a retroversion since then. Appendectomy for ulcerative appendicitis at that time. Complete breakdown since then, with headache, backache, lack of mental concentration, and coördination. Stomach trouble and constipation since childhood and numerous "bilious attacks." At seventeen severe obstipation and no movement for thirteen days. Ten years ago, hematemesis. Markedly toxic; excess of food remnants; fermentation and putrefaction in feces; excess of indican in urine. Radiographs showed no enteroptosis but marked cecal constipation. Uterus retroverted and fixed. Medical treatment for intestinal toxemia was diet and mineral oil and colon vaccines, the latter giving the most help.

Operation, January 1916. Strong bands across ascending colon severed and adhesions of uterus to rectum relieved and redundant portion of cecum removed. Recovering. Noteworthy was the good result from the autogenous colon vaccines.

The writer wishes to express his gratitude for the valuable assistance of Dr. Arthur Mandel for the clinical pathology, Dr. Albert G. Bennett for the bacteriology, and Drs. Leon T. Le Wald and John W. Draper for the radiographic work. To Drs. J. M. Lynch and John W. Draper he is deeply indebted for the opportunity to study the operative side and for their operative skill on his cases. Dr. John Douglas and Dr. Burton J. Lee have also operated on some of the patients.

It would scarcely be proper to close without mentioning the character and number of operations in this series of cases. There were 31 abdominal sections. Appendectomy, chronic or subacute, 9; colon suspension, 9; for reconstruction of the colon (Lynch and Draper), 8 (all recovered except one with advanced toxemia and toxic arthritis, who died with a septic peritonitis); ileostomy, 1; colon suspension, appendectomy, cholecystectomy, and adhesions, 1; plication of cecum, 1; colon suspension and nephropexy, 1; gastroenterostomy and Lane's kink, 1.

In conclusion, it is evident that the closest kind of coöperation should exist between the physician and surgeon, as no real internist should fail to be a student of actual conditions.

The view-point should be neither surgical nor medical in the old sense, but should be critical and unbiased by old dogmatic views. The cure of the patient should not end with the operation. Most of the failures in the past have been due to lack of coöperation between the physician and surgeon, and often caused by the improper following up of the patient.

CHART OF TEN CASES PRESENTED IN DETAIL.

Patient.	Roentgen-ray findings.					Bands.	Congenital anomaly; remarks.	Sex.	Age.	Bowel history.				Feces, excess of			Indican, urine.	Symptoms.				Loss of weight.	Crepitation of cecum.	Preventive appendectomy.	Previous operations.	Treatment.			Results.
	Enteroptosis.	Residual stomachs.	Residual cecum.	Residual sigmoid.	Colon empty.					Diarrhea.	Constipation.	Regular.	Colic mucosa.	Food remnant.	Putrefaction.	Fermentation.		Mental.	Physical.	Nerve.	Flatus.					Operative.	Medical.	Colon vaccine.	
W. W. B.	$+^{3}$	0	+	+	3d +	Volvulus	High blood-pressure	♂	33	–	$+^{3}$	–	+	–	+	+	–	+	$+^{2}$	$+^{3}$	$+^{3}$	40	+	+	–	Reconstruction of colon	+	+	Well (3 years); blood-pressure, normal; nature careless.
C. B.	0	$+^{2}$	+	?	?	Ileal kink	Insane; severe toxemia	♀	32	–	–	+	–	–	+	+	$+^{3}$	$+^{3}$	$+^{3}$	+	$+^{2}$	?	?	–	–	Reconstruction of colon	+	+	Well (2 years); toxic nephritis disappeared.
M. D.	+	+	$+^{2}$	–	2d +	. . .	. . . .	♀	27	–	$+^{2}$	–	–	Not exam.			+	–	+	–	+	10	+	–	Suspension of uterus	Reconstruction of colon	+	+	Well (1 year).
R. B. E.	$+^{2}$	0	$+^{2}$	$+^{3}$	3d $+^{2}$	. . .	Melancholia	♀	34	–	$+^{2}$	–	+	Not exam.			+	$+^{3}$	+	$+^{2}$	+	+	+	+	Ovarectomy; peritoneal adhesions	Reconstruction of colon	+	+	Improved (16 mos.).
C.	0	0	+	0	3d +	. . .	Volvulus; migraine	♀	38	+	+	–	–	Not exam.			+	–	$+^{2}$	+	$+^{2}$	40	?	–	Curettage	Reconstruction of colon	+	+	Well (3 years).
H. R.	+	–	$+^{3}$	–	3d	. . .	. . . .	♂	25	–	$+^{2}$	–	+	Not exam.			–	+	$+^{2}$	–	+	5	+	–	–	Reconstruction of colon	+	–	Well (3 mos.).
W. L. R.	$+^{2}$	+	+	–	3d	. . .	Obsessions.	♂	35	+	+	–	–	+	$+^{2}$	$+^{2}$	N	$+^{3}$	–	+	$+^{2}$	0	+	–	–	--	+	+	Marked improvement (6 mos.).
J. F. S.	$+^{3}$	$+^{2}$	–	+	?	. . .	Similar condition in daughter	♀	45	–	$+^{2}$	–	–	Not exam.			+	$+^{2}$	$+^{2}$	$+^{2}$	+	22	+	–	R. nephropexy	Suspension of colon	+	+	Well (3 years); slight constipation and toxemia; gain 20 pounds.
B. R.	+	$+^{3}$	–	?	3d	. . .	Chronic appendicitis	♀	40	+	+	–	+	+	0	0	N	–	+	+	+	30	$+^{2}$	–	. . . .	Appendectomy	+	+	Improved medically; Well 6 mos. after operation.
R. C. D.	0	0	$+^{3}$	?	?	Across ascending colon	Perirectal adhesions; retroflexed uterus	♀	34	+	$+^{2}$	–	+	$+^{2}$	+	+	$+^{2}$	$+^{2}$	$+^{3}$	$+^{3}$	$+^{3}$	3	+	+	. . . .	Hysterectomy; adhesions and bands	+	+	Improved by vaccine and operation 5 (wks.).

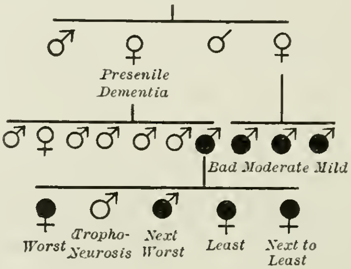
What conviction is uppermost from this study of 136 cases? Unquestionably that diagnosis is the all-important factor. Obviously this cannot be made either simple or sure until much more is known regarding the cause of intestinal toxemia. Most to be desired is a unified effort from the medical clinic, from the operating room, and from the laboratory. In this way only shall we find all of the truth.

A FAMILY WITH MYOTONIA, PROBABLY INTERMITTENT FORM OF THOMSEN'S DISEASE.

By Noxon Toomey, M.D.,
PHILADELPHIA, PA.

The following cases illustrate a myotonic family. They are interesting because Thomsen's disease is rare and very few cases of the intermittent form have been reported. Whether acquired myotonia, paramyotonia, Gower's type, myotonia with atrophy, and intermittent myotonia are forms of Thomsen's disease is not known. Recording forms met with may eventually throw light on their relationship, and it is to help to that end that this paper is compiled. Due to a lack of facilities no attempt at a pathological study has been made. The case histories were obtained with few if any leading questions, and are really narrations by the sufferers. Catch questioning elicited no contradictions.

The cases are eight in number and are in three generations. Three cases in a collateral line could not be seen by me. In the three generations there were nineteen persons over one year, thus about 40 per cent. of the family was affected. Those who have married have had large families, most of their children growing to adult age. No evidence of syphilis or rheumatism can be found in the family. The accompanying figure shows the involved collateral line. The black figures indicate the members affected.



The cases studied are in an industrious, self-respecting family of well-marked Irish descent. The family is of the unskilled labor class but the members are intelligent and always have had more than the necessities of life. Except for the dystrophy, they have been free from sickness and are otherwise well developed and nourished. They live in South Baltimore, but come from the country. Their house is of two stories with fair light and air and good plumbing, heat, and dryness. The neighborhood is not congested.

The three cases not seen by me were described by the head of the family that I studied. My informant grew up with his cousins and knew their condition well. Their cramps were just the same as his, except that the older two had it worse than he did. The three "always had the trouble." In the oldest the condition is getting worse. The other two died of a chronic pulmonary disease after middle life. Their myotonia did not get worse after early manhood. "They did not have it as bad as their older brother, and the youngest of the three had only a little trouble in walking. The oldest brother had it so bad that he often could not walk and they would often have to go out in the field to bring him in. The next youngest could hardly walk at all when he had it." The myotonia in the three was transitory, as in the five cases that I saw.

In the cases examined the father has had it as bad as any of his children. Of the children the oldest has had it the worst. The second oldest is not affected. The next, Martin, has it worse than the youngest children, Rose and Agnes. There are three children dead, one of pertussis at seven months; the next at four months, cause unknown; the third was a two months' abortion. There are no mental peculiarities, temper, etc., in the family, and no evidence of tuberculosis, syphilis, rheumatism, neoplasms, or hysteria. Labors were all normal.

Father, aged forty-four years. Mother was "weak minded after she was fifty-five years old." Paternal side normal. Has been well except for measles, pertussis, mumps, and dystrophy; has never worked around lead, etc. Married at twenty-five. Was a street-car motorman for six years; gave up job for family reasons. Since then has worked at various moderately hard manual jobs in open air. Food and habits negative, except wife says "he is a great eater and a great one to salt his food." Drinks beer occasionally; never drunk. He says: "When I drink more beer than usual it makes my condition better."

Present Illness. "Was fourteen years old when I had first spell. Was playing base-ball one winter evening. Came home overheated. Later went to bed and slept naturally. Next morning I woke up and found I could not move myself from waist down. Could not get out of bed alone. I had great difficulty in making legs move, but could move them by great effort by end of first day. I had no pain, fever, or other discomfort. The legs got better the more they were moved, and in two or three days use of legs was regained. Second attack was about one year later, and was the same as first. As I grew older they came closer together; some years I would have four or five attacks; sometimes twice in same month; sometimes not for six or nine months; no regularity at all. Were more frequent from my fifteenth to twenty-second year, then stayed about the same until I was thirty-five years old. In this time I would average about four or five times in a year. Stiffness would last four or five days. About every two months I would have slight attacks lasting a day only; all spells lasted a day or more. Fourteen years ago I was laid up for eleven days, in which I could move my legs but very little. For past eight or nine years they have not been coming as often and are not so long or hard."

Description of cramps: "I have not the least idea what causes them. Spells come on with no warning at all; mostly during sleep. We often talk about the cramps, but it has had no effect in producing them. I get them in hot weather as well as cold. They come on with drawing up of the belly, but no real pain. I wake up and find I cannot get out of bed for a while because my legs are stiff and will not move. The muscles never get hard for a time, but they feel too short to stretch out leaders. Even now if I sit down for three or four hours I will not be able to get up at first or will get up feeling very stiff in the legs, which must be walked off by a few minutes' exercise. When sitting still for some time I get jammed up a little and get stiff, but pay no attention to it; but get a cane and walk it off by moving around the room. I have often gone to work feeling stiff, but could stand on feet all right; but I would not have worked those days if I would have had to walk much. Sometimes during the day the stiffness would not get better by standing and I would have to walk stiffness off. I would never get worse during a day at the motor, but sometimes I would feel very tired. When I worked the day out I would feel better at night than in the morning. The longer I worked the better I felt, and the better I could move myself. During a spell I cannot take long steps at first and can only move slowly. The calf of my legs seem stiffest, and is harder than other places. Sometimes when I have been reading for a good while, when I start to look up I find my eyelids will go up but my eyes cannot; they will stay looking at the paper for a few minutes even though I want to look up, or if I want to look down my lids will not go down with my eyes. Sometimes when I want to let go of a thing I cannot do it for a moment my hand being clenched tight."

The leg muscles are affected the oftenest, the external ocular muscles next most frequently, and the hands the least. Abdominal muscles seem to be involved in some attacks. As to treatment he said: "My legs never lose color or are cold. Rubbing them with camphorated oil or anything else has never made them better, and I have found that nothing will help me except to walk stiffness off."

Physical Examination. Habitus, frame, and panniculus good. Muscles well developed, particularly of lower extremity, but are not hypertrophic. Strength in proportion. Pupillary reactions, arteries, and functional capacity of heart normal, no organic lesion. Teeth in poor condition but physically is otherwise negative. Gait and station, muscle sense, and sensation to touch and pain normal. Reflexes active and equal on two sides; no abnormal reflexes. There is no ataxia, astereognosis, trophic changes, etc. Electrical stimulation of muscles and ulnar nerve normal. Arm and leg muscles do not react to light tapping but marked percussion produces a quick, quite hard contraction that lasts from four to eight seconds. The contraction disappears gradually lasting longest in the belly of the muscle. Percussion of peronei, extensors of the hand and occasionally hamstrings and rectus femoris produces a distinct grooving of skin lasting a few seconds and a quick extension (or flexion) that is well sustained, at least six seconds elapsing before the fingers, foot, etc., return to former position. Reflex contractions do not cause cramps. No muscles atrophied.

Katheryn F., aged eighteen years. Past history unimportant. Development and puberty normal; leads moderately active life. Habits negative except prefers salty foods. Had worked as a bottle-filler for the past three years.

Present Illness. "First spell occurred at two and a half years; it lasted about a week. Consisted in legs getting so stiff when she tried to walk that she would fall down, particularly going down stairs. Left side was weaker, so that she could not stand right, but that got better right along. After first attack spells came on at night only; she would be so stiff in legs in morning that she could not get out of bed. I used to rub her legs, then she could move them a little, and after that the more she moved them the less the stiffness became. She used to have two spells a month up to five years old; would have them in hot weather same as cold. Spells of morning stiffness were all the same; they would last three days, first two days she would be helpless. Some were accompanied by nausea and fever and usually costiveness, but never looked sick enough to be the way she was." Was never unconscious, and had no ataxia, twitching, pain, or paresthesias, etc. "After sixth year had spells quite irregularly every six months to a year. Spells were the same as before, but were not so hard; they then kept on getting better. She has had no stiffness in her limbs for past five years, except three weeks ago, but has had attacks in her hands, eyes, and neck. She soon learned that the more she walked the better the cramps in her legs got."

Description of cramps by patient: "In cloudy weather come oftenest, have had two or three spells of stiff neck or right arm for many years. Stiffness lasts five minutes. While neck is stiff it pains me terribly; can move neck a little but it swells out and gets hard. When I would rub it and move it around it would go down. Each time I moved neck the stiffness got better. Sometimes neck is stiff in morning but I think it is because I lie crooked. When neck is stiff it is only one side at a time. The left side was always the worse.

"Once a month or so I have stiffness in eyes, so that when I have been reading for some time and want to look up my lids will go up, but the eyeballs will be glued down and I cannot move them up, or sometimes when I am looking up and then look down the upper lids will not come down, but will separate from the eyes. Stiffness may last a minute. When I sometimes try to grab on to a thing quickly some of my fingers get so stiff that I cannot hold on. Only one finger draws up at a time, usually the index finger; both hands are affected equally. Not started by a hard squeeze. Fingers are never drawn back (hyperextended).

"For several years I have had cramps in the legs that draw up my toes; sometimes only the big toes; toes become stiff, and it hurts me in the hollow of my foot. Both feet are affected the same. The only stiffness in upper limbs that I have had for five years was three weeks ago, and I think it was brought on by sitting still for four hours. I was feeling perfectly well and stood up without trouble, but when I started to take the first step I found I could not; the legs were so stiff I could not straighten them out. The legs felt as if the muscles were cramped up and not long enough to stretch out the feet. It hurt a good deal. Each step I took the better the stiffness got, but it was not completely gone for two weeks. Every time I would sit still for some time it was the same thing over again; I could stand up all right, but when I walked the muscles were hard and not long enough to stretch out, so I had to walk real slow and take small steps. At first it was worse in one leg, and I had to limp for a short time. I am certain that during those two weeks I was always stiffer after sitting still a little, and the more I would walk the better the stiffness got. I have never noticed the arm and neck or legs and neck affected at a time. The attacks are not like when your foot goes to sleep."

Physical Examination. Habitus normal; musculature above average, but not hypertrophic. Strength in hands and legs less than was expected. Complete physical examination not permitted. Sensation and reflexes in extremities; gait and station normal. Nerve reactions normal. Faradic excitation and percussion of muscles of extremities produced a slow tonic contraction, lasting four to six seconds. With galvanic current, kathodal closing contraction not quantitatively reduced. Current not strong enough for kathodal opening or anodal contractions. No muscles atrophic or paretic.

John F., aged seventeen years. Chorea at eight years. Has never had myotonia. "Is the only child that resembles mother's family, which he does decidedly, being red-haired like them." Is thought to have frozen hand. During cold weather the past four years the right hand will become perfectly white distal from metacarpus. During the attack, which lasts a variable time, there is almost complete anesthesia and analgesia. There may be paresthesias as ischemia wears off. Physical examination is negative. Muscle reactions are normal.

Martin F., aged eleven years. Past history and habits negative. "Is a great one to salt food. Stiffness began when he was five years old. Used to average about two spells a month; would be only of a few minutes to an hour's duration. Spells come irregularly; he is getting a little better of late. There has been no noticeable change (in clinical course); legs, arms, and neck muscles have been involved about equally for a number of years. The muscles in the back of his legs usually get harder than the other muscles, but when he has it in his neck the muscles stand out like two boards. When his legs get so stiff he cannot walk I rub them with liniment or camphorated oil, but I have found that hot water does as well as anything. When he is in a stiff spell he has to drag his feet after him for a minute, and when he goes up stairs I have to support him up the first steps and sometimes the whole way."

Patient says: "I do not have it much in hot weather; had only one spell last summer; when I go out in dampness it brings it on. When I sit still and sometimes when I come into the house the stiffness comes on. Then I have a hard time in getting up and usually fall; but sometimes I do not. Most of the times it makes me stiff in the legs and sometimes in the legs and arms, so I fall easily. I guess I have to go about ten steps before stiffness gets better. Rapid walking has never brought it on. I cannot always walk fast, but when I can I am always at my best. It comes on usually when I stub my toe, and then I usually fall because my legs become as stiff as sticks. Up to about a year ago I used to often wake up stiff in the morning and would have to kind of roll out of bed, then get a stick and walk around the room a few minutes. My neck gets stiff mostly when I look around quickly. When I am stiff the muscles get hard, but only the neck muscles stand out any, sometimes for ten minutes. When I grip anything real tight pretty often I have to hold it for about ten to fifteen minutes before I can let it go, but my hands never get white like John's."

Physical Examination. Well built, with good muscular development and strength in proportion. General physical negative except for several carious teeth, adenoids, and slightly enlarged tonsils and cervical glands. No thymus dulness. Sensation, etc., normal. Reflexes quite active but equal; no clonus or abnormal reflexes. Gait normal. Muscular reactions: light percussion causes slight contraction of belly of muscle. Heavier percussion of extensors causes a slow contraction lasting four or five seconds, followed by a slower relaxation. Percussion of peronei causes a sustained ever-sion of foot. Hard percussion two inches above patella causes a slow extension of leg, followed by an equally slow flexion by gravity. Faradic and galvanic stimulation normal. Blood picture: normal. Urine: normal except for sp. gr., 1.008 to 1.010, two specimens. Von Pirquet negative.

Rose F., aged nine years. Well except for measles and tonsillitis past three years. Mother believes the stiffness comes with the tonsillitis, which is febrile and accompanied by dysphagia and anorexia. "She has had it less often and lighter than the others, and it does not last as long." Patient says: "I have had disease about two years; spells have not come as often this year as they used to. In December, 1914, I was in school and my legs got so stiff I could not walk, the stiffness lasted half an hour. Two months later I suddenly got stiff at the head of the stairs and had to be carried down them. The stiffness lasted ten minutes, then I walked around and got better. From then until December 24, 1915, my legs have been stiff once, arms stiff twice, and neck stiff once. December 24, 1915, had stiffness from knees down, lasting fifteen minutes. January 5, 1916, neck was so stiff that it could not be moved for about five minutes. During attacks right side is often stiffest. The muscles do not get real hard, and spells never hurt at all. When I feel my legs get stiff I have to get up and walk slowly and take little steps, which make it go away quicker, but stiffness usually gets better of a sudden. About two hours after I have a spell Martin and Agnes will have the same stiffness." Rose has had no paresthesias, trouble in standing, no stumbling, falling, involvement of ocular muscles, etc.

Physical Examination. Frame and panniculus good. Musculature fairly well developed, strength equal. Slightly enlarged tonsils, no adenoid enlargement. Cervical glands barely palpable, indurated. Thyroid normal, no thymus dulness. Functional capacity of heart and lungs normal. Abdomen and remainder of examination negative. Blood picture normal except for hemoglobin, 75 per cent. (Sahli). Urine (several specimens) normal except for heavy amorphous urate cloud on admission to hospital. Wassermann and von Pirquet negative. Took ether well; developed no acetone. Nerve reactions normal. Muscle reactions: studied during an attack of myotonia. Child was found sitting on edge of chair with thighs extended, due to difficulty in overcoming hamstring spasm. Legs flexed, toes extended, but less rigid. Whenever asked to walk she slid off chair sidewise and attained erect attitude with some difficulty. She limped at first, due to left leg being more strongly flexed. The steps at first were slow and manifestly difficult, but not greatly shortened. There was no pain or adductor spasm. After seven or eight steps the spasm gradually broke and the patient gained a normal gait, precluding spinal syphilis. Thigh and leg muscles were hard, and firm pressure made them much harder than the arm or trunk muscles. Passive muscular movement and reflex contraction normal and excited no myotonia. Marked percussion of unaffected muscles produced a slight myoidema; harder percussion produced a slow contraction lasting about eight seconds. Light percussion of the affected groups, the hamstrings and quadriceps, produced myoidema. Moderately hard percussion of rectus femoris and bellies of vasti produced a slow extension of the leg that lasted ten seconds before being gradually flexed by gravity. Hard percussion of hamstrings produced a tonic contraction lasting ten seconds to an hour, and during a light ether anesthesia they could be felt as hard cords. Hard percussion of hamstrings produced a grooving of skin instead of a mounding. The myobradia was most marked in the rectus femoris. No paresis or atrophy of any muscles.

The unaffected groups were less excitable to faradic stimulation than normal. They were slightly hyperexcitable to kathodal closing, but anodal closing was not obtainable. The affected groups would not contract to strong faradism. In these muscles a thirty-volt wave-free galvanic current produced on kathodal closing a slow tonic contraction that lasted about a minute after cessation of stimulation. Anodal closing contractions were nearly as strong as the kathodal. Opening contractions not obtainable. The attack of myotonia lasted about six hours and then disappeared quickly. During the six hours the thigh muscles were somewhat less hard after walking about wards, only to become stiff after a few minutes' rest.

Agnes F., aged six years. Past history and habits unimportant. "Has had no sore throat and has not been sick when she has had the cramps. She has had the trouble past three years, is not getting worse. First noticed drawing up of all fourth fingers and toes. Spasms will last two minutes. Are noticed mostly at breakfast table; will average two or three cramps a week. I think Agnes gets it mostly in cold weather; her arms are mostly affected, then her legs, then her neck. She is clumsy and stumbles easily; she falls frequently, particularly down steps. If she would glance around quickly her eyes would get so stiff that she could not shut them. When Agnes gets stiff in her legs she trys to stand up and walk. Sometimes she falls at first and may need holding for the first few minutes, but after she gets walking around a little she gets better and then is shortly all right. When she has the cramps she has no pain at all, but muscles get hard, particularly when she has them in the neck; then the muscles will stand out like boards. If I walk her fast she gets spasms in her muscles and cannot move her legs right; coming up here, when I walked her fast, she got stiff in her legs and I thought we would never get here. She had to take slow, short steps, but after walking some the spasm went away and she walked all right. She has it oftener than the others, but not as bad as Katheryn, may be because the child is never still the whole day, but is always on the go."

Physical Examination. Strong, well built, and nourished. Hemoglobin and blood picture normal. Small adenoids; tonsils slightly enlarged. Uncorrected hypermetropia of about D. 2. Thyroid normal; no thymus dulness. Von Pirquet negative. Knee-jerk obtained with reinforcement, equal; sensations, etc., normal. Electrical reactions, gait, and station normal. Percussion of extensors, but more particularly flexors, produces a grooving of skin and a slow movement of digits. Fingers are maintained in flexion (or hyperextension) for about fifteen seconds before returning to previous position.

LITERATURE.

Nearly three hundred articles on Thomsen's disease are listed in the Catalogue of the Surgeon-General's Library and the later volumes of the Index Medicus. About four hundred cases have been reported, mostly cases with constant myotonia and of the hypertrophic and atrophic types.

Metabolism studies are recorded in Am. Jour. Med. Sc., vol. cxli, and Arch. Int. Med., August, 1914.

Some of the other important articles consulted are in: Quart. Jour. Med., April, 1910, January and July, 1912, January, 1915; Edinburgh Med. Jour., N. S., vol. xi; Montreal Med. Jour., vol. xxxvii; Allbutt's System; Osler's Modern Medicine.

The following treat of the intermittent form:

Erb. Die Thomsen'sche Krankheit., Leipzig, 1886.

Pelz. Arch. f. Psychiatrie, vol. xlii.

Martius und Hansemann. Arch. f. path. Anat., etc., vol. cxvii.

Mingazzini e Perusini. Rev. d. patol. nerv., vol. ix.

Lord. Boston Med. and Surg. Jour., vol. cxlii.

REVIEWS

Progressive Medicine. Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, Professor of Therapeutics, Materia Medica, and Diagnosis in the Jefferson Medical College; Physician to the Jefferson Medical College Hospital, Philadelphia, etc. Assisted by Leighton F. Appleman, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia, etc. Vol. I, March. Pp. 354; 19 illustrations. Vol. II, June. Pp. 482; 113 illustrations. Vol. III, September. Pp. 394; 18 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

Thus far during this year there have appeared three volumes of this well-known and justly popular quarterly review of medical progress. The March number opens with a discussion of the surgery of the head and neck by Charles H. Frazier. Most of his attention is directed toward the cranial nerves and the brain. The article concludes with a section devoted to the mammary gland. A most interesting and instructive article on the surgery of the thorax has been contributed by George P. Müller, who devotes a large proportion of his article to a discussion of empyema. The longest article in this volume, as well as one of the most enlightening, is John Ruhräh's contribution on infectious diseases. Over 120 pages is devoted to this all-important and comprehensive subject. A great deal of work during the past year has been done upon the infections, and Ruhräh's article is replete with instructive suggestions and observations. The subject of diseases of children is taken up by Floyd M. Crandall in about 30 pages. As usual, the diarrheas of children and the dietetic problems of infancy receive considerable attention. George B. Wood furnishes the review of rhinology and laryngology, devoting particular attention to the accessory sinuses and tonsils. A short review of otology by Truman Lawrence Saunders concludes this volume.

Volume II opens with a 34-page article by William B. Coley on hernia. This is followed by a thorough discussion occupying 146 pages of the surgery of the abdomen by John C. A. Gerster. He lays stress upon the timely subject of gunshot wounds of the abdomen in war. Various affections of and operations upon the stomach, duodenum and small and large intestines are then taken up in order. He devotes great care to a review of recent work upon the liver and bile passages, and concludes his article by a discussion of the surgery of the spleen, a subject which has recently attained considerable importance. Under gynecology John G. Clark furnishes his usual interesting, complete, and valuable contribution. He again accords cancer of the uterus first place, although non-malignant conditions of the uterus are also discussed with unusual thoroughness. Alfred Stengel covers a wide range of important medical subjects in an article of 122 pages. Diseases of the blood are first taken up, and the spleen and hemorrhagic diseases are then discussed with a thoroughness justified by the importance which these conditions have recently assumed. In addition to the thyroid and parathyroid glands it is gratifying to note the space which is devoted to a consideration of affections of the pineal gland. He concludes his article by a thoroughly up-to-date review of diabetes and gout. The last article in the volume is by Edward Jackson on ophthalmology. In this the affections of the eye are taken up under the various anatomical divisions of the organ.

The third volume, which appeared but a few weeks ago, contains an article by William Ewart on diseases of the thorax, including the heart, lungs, and bloodvessels. Ewart enters first into an instructive review of the respiratory function. He then discusses a number of interesting recent observations upon physical signs and methods of physical diagnosis. Next, he takes up pulmonary tuberculosis and various respiratory and pulmonary affections. Much important material is reviewed under the subjects of the blood, the bloodvessels, and the circulation, among the most interesting of which are the "soldier's heart," various unusual diatheses and syndromes, vagotonia, shock, and "heart seizures." As usual, William S. Gottheil's contribution on dermatology and syphilis is decidedly enlightening. Autoserum therapy, heliotherapy and pellagra are some of the subjects particularly dwelt upon. His contribution on syphilis is especially worthy of note. Edward P. Davis gives a comprehensive review of recent advances in obstetrics. Pregnancy and the toxemia of pregnancy occupies a large portion of his contribution. The placenta, the puerperal period, labor and its management, obstetric surgery, and finally the newborn are all dealt with in detail in the course of this unusually long article of nearly 200 pages. The final section of the volume is a scholarly contribution by William G. Spiller on diseases of the nervous system, in which he lays particular stress upon the subject of brain tumor, cerebrospinal syphilis, syringomyelia and many other important complicated neurological subjects.

A comparison of these three volumes of *Progressive Medicine* leaves little to choose. In every instance the contributions are furnished by men of acknowledged prominence in their respective fields, and throughout the preparation of the articles has been conducted with praiseworthy care. G. M. P.

OPERATIVE MIDWIFERY. A GUIDE TO THE DIFFICULTIES AND COMPLICATIONS OF MIDWIFERY PRACTICE. By J. M. MUNRO KERR, M.D., C.M. (Glas.), Professor of Obstetrics and Gynecology, Glasgow University (Muirhead Chair); Obstetric Physician, Glasgow Maternity Hospital; Gynecolosist, Royal Infirmary. Third edition. Pp. 711; 308 illustrations. New York: William Wood & Co., 1916.

THE importance of the surgical aspect of modern obstetrical practice receives its full due in the volume before us. That it has reached a third revision in seven years is a measure of the advances in the art of obstetrics during this time, and none the less an unspoken commendation of the book itself. Dystocia has been considered in a most comprehensive manner from every stand-point. The operative maneuvers in delivery, and also those precedures necessitated by complicating conditions of the pelvic organs, are described in detail. The chapter on the use of forceps would be of little use to American physicians, as the performance of the forceps operation with the patient in the lateroprone position is not familiar teaching in this country. In a similar manner the illustrations portraying the use of the various models of forceps is confusing.

Extraperitoneal Cesarean section is looked upon with disfavor. The merits of the operation in presumably infected cases necessitating supravaginal delivery are overlooked, and it is judged rather by a comparison of the scar resulting in the lower uterine segment with the higher scar of the classical operation. Accidental hemorrhage, premature separation of the normally situated placenta, and in view of the pathology, intramural hemorrhages, are considered as forms of pregnancy toxemia. In order to lessen the maternal mortality from the often uncontrollable postpartum hemorrhage, the author recommends hysterotomy followed by abdominal hysterectomy. There is a well-written chapter devoted to parturitional injuries of the child. This third edition fully maintains the high standard established by its predecessors. P. F. W.

DIE THERAPIE DER HAUT: UND VENERISCHEN KRANKHEITEN. By Prof. Dr. J. SCHÄFFER in Breslau. Pp. 450; 87 illustrations. Berlin and Vienna: Urban and Schwarzenberg.

DR. SCHÄFFER'S excellent volume is divided into two distinct parts, the first, dermatological and the second, venereal diseases. The various remedial cutaneous agents are discussed under the following headings: The technic for handling various diseases; alleviating hints for the assortment of medications; the different methods of application; salves and oils; salve bases; dusting powders; mixtures that have to be shaken before applying; plasters; varnishes; zinc adhesives; soaps; and waters.

Physical healing methods are detailed under heat applications; light therapy; surgical interference; diet; and internal treatment. After the various external and internal methods of treatment have been discussed, the writer applies the various means to the individual cutaneous outbreaks; arranging the latter diseases alphabetically.

Two hundred and eighty-five pages are devoted to dermatological conditions, one hundred and four of which are devoted to the various external applications and internal remedies and the remainder to those applicable to the individual cutaneous outbreaks; fifty-five pages treat of gonorrhea, in its various stages and complications, ulcus mollus, inguinal buboes, etc.; and seventy-six to the treatment of syphilis.

The treatment of syphilis is amplified by the technic of microscopical spirochetal investigation, serological studies, the method of obtaining the blood from the vein (venous puncture), and the clinical meaning of the Wassermann test. Syphilitic therapy is interestingly described, including the mercurial, iodide, salvarsan and neosalvarsan methods. The various procedures advocated are detailed according to the stage of syphilis that is to be treated, including the earliest and latest manifestations of the disease, the congenital form of the affection, the general hygiene of the patient, and the local therapy of various lesions.

The eighty-seven pictures in the text illustrate graphically the various methods of applying the medicaments, the injections, roentgen-ray, Kromayer lamp, dark-field illumination, the Wassermann test, etc. F. C. K.

MOSQUITO CONTROL IN PANAMA. THE ERADICATION OF MALARIA AND YELLOW FEVER IN CUBA AND PANAMA. By JOSEPH A. LE PRINCE, C.E., A.M., and A. J. ORENSTEIN, M.D. Pp. 335; 100 illustrations. New York and London: G. P. Putnam's Sons, 1916.

THE book is written in semipopular style and may be read by anyone who has an interest in the great engineering feat of constructing the Panama Canal.

The work is considered from two standpoints, as it relates to the campaign against malaria (Part I, Anti-malarial Campaign), and to the fight against yellow fever (Part II, The Yellow Fever Campaign).

The campaigns against malaria and yellow fever in the Canal

Zone were conducted by the authors under the direction of General Gorgas, and full details are given of the problems and how they were met. Mr. Le Prince had served under General Gorgas in cleaning up Havana, and the experience gained in this earlier work was invaluable in the prosecution of the more extensive and more difficult work in the Canal Zone.

Fundamentally the campaigns against the mosquitoes concerned in the transmission of malarial and yellow fevers may be divided into four principal divisions: (1) drainage of all bodies of water that could be so diverted, the construction of concrete gutters for the smaller water courses, and the removal of vegetation from the banks and the beds of the streams; (2) the application of oil to all bodies of water and to flowing streams in order to kill mosquito larvæ; (3) the screening of all buildings to protect against mosquitoes and the trapping and killing of mosquitoes that had entered the houses; (4) the general cleaning of habitations and towns.

It was a fortunate circumstance that at the time when the United States took over the construction of the Panama Canal there had developed a knowledge of the agency of mosquitoes in the transmission of malaria and yellow fever, otherwise (as the authors state) the great engineering work would have been a failure as it was under the supervision of French engineers who did not have this knowledge to aid them.

The greatest honor connected with the completion of the canal must be given to the intelligent sanitary engineers who applied the knowledge which experience had then shown to be imperative if the undertaking was to be completed without unnecessary sacrifice of human lives.

The illustrations show clearly how the important work of mosquito extermination was carried out.

This book will serve as a reliable guide to those engaged in similar work elsewhere. It is possible to rid any community of malarial and yellow fevers at a cost which will be infinitely less than that entailed on such a community by these two diseases.

D. H. B.

LEUKEMIA OF THE FOWL: SPONTANEOUS AND EXPERIMENTAL. By HARRY C. SCHMEISSER, M.D. Pp. 34; 4 plates. Baltimore: Johns Hopkins Press.

THIS monograph is an extensive and complete discussion of that interesting condition, fowl leukemia, which may be transmitted directly from one fowl to another by means of injection of an organic emulsion. The injection causes a disease similar to that which is spontaneously developed, and the changes which are produced are comparable to those which are seen in the corresponding disease of human beings.

J. H. M., JR.

GESCHICHTE DER NASENHEILKUNDE VON IHREN ANFÄNGEN BIS ZUM 18 YAHRHUNDERT. By KARL KASSEL (Posen).

THIS work of 476 pages presents the subject of the history of rhinology with the characteristic German love of detail. The author starts with the Egyptians, Assyrians, and Babylonians and their methods of treating diseases of the nose. Considerable space is given to the Grecian and Roman philosophy and medicine, perhaps in too great detail for the casual reader. Hippocrates and Galen, of course, are given great prominence. The middle ages start with the Arabs (608 A.D.) and end about 1500.

The third chapter on the later times (Neuzeit) begins with Paracelsus and continues to the seventeenth century.

The work will never find general popularity on account of its minutiæ, as it is practically an encyclopedia on the subject, but will probably be the standard reference on the history of rhinology for all time. G. M. C.

VIEWS ON SOME SOCIAL SUBJECTS. By SIR DYCE DUCKWORTH, Bt., M.D., LL.D., Fellow and Treasurer of the Royal College of Physicians, London; Consulting Physician to St. Bartholomew's Hospital. Pp. 320. New York: The Macmillan Company.

THESE essays represent the views and impressions that a medical man has gathered during the greater part of a lifetime, a lifetime devoted for the most part to the practice of medicine, but broad enough to consider and to engage in other activities. As their titles imply, they represent views of social subjects, most of which have some relationship to medicine, though a few have no connection whatsoever with medicine. They will well repay the reader in the delightful hour that they will give. J. H. M., JR.

INFANT HEALTH. A MANUAL FOR DISTRICT VISITORS, NURSES, AND MOTHERS. By J. S. C. MACMILLAN, C.M.B., A.R., San. I. Pp. 128; 12 illustrations. London: Oxford University Press.

THIS manual is delightfully written, and may be read with profit by any lay or medical person interested in the betterment of the child. Its teachings and advice are mostly fundamental, but so clearly set forth as to impress them with force. The author considers in a brief way the necessary knowledge of anatomy; the simple things to know and care for in pregnancy; the keeping of both the mother and child well; the proper hygienic procedures for the baby.

The author is to be commended for not going too deeply into the subject of infant feeding in a book of this scope, especially when it is written essentially for the non-medical reader. A. G. M.

Diagnostic Methods. By Herbert Thomas Brooks, A.B., M.D., Professor of Pathology, University of Tennessee. Third edition; pp. 965. St. Louis: C. V. Mosby Company, 1916.

This is a very brief guide in history-taking, and the making of routine physical examinations and laboratory tests necessary for students in clinical pathology. The new third edition has an added chapter on the technic of staining and examination of smears, most important exudates, etc. The author advises, along with the use of his work, that the reader should study some extensive work on clinical diagnosis.

The book is similar to many others in the same field. It apparently serves a local purpose in the author's university, and can hardly appeal to the man outside of these medical halls. Some of the newer renal functional tests might have been added with profit to the reader. The type is clear; the paper is good; the binding is excellent—all that could be wished for in a well-constructed book. The directions are accurate, brief, and up to date; all features that make for a desirable laboratory guide. T. G. S.

The Pathology and Treatment of the So-called Nervous Asthma. By J. B. Berkart, M.D., Late Physician to the City of London Hospital for Diseases of the Chest; Corresponding Member of the Société Royale des Sciences Médicales et Naturelles de Bruxelles, of the Société de Médecine of Paris, etc. Pp. 54. London: Humphrey Milford, Oxford University Press, 1916.

Berkart in this small volume draws a sharp line of distinction between that form of paroxymal dyspnea in which the disturbing factor is "a transient obstacle in the bronchial tree" and that in which the air passages are perfectly pervious, speaking of the latter as "the so-called nervous asthma." The distinguishing feature of this type is the complete lack of physical evidence of any impediment to the ingress and egress of air during the attack. It generally follows, he believes, rickets which has affected chiefly the spine, only slightly the chest and lungs, and is based upon an endogenous neuropathy. His treatment is therefore directed primarily toward the neuropathic disposition, and his suggestions for the management of such a condition are eminently logical and at the same time practical. He wisely taboos the widespread nasal treatment of these cases and believes the alleged anaphylaxis of eggs and milk has not been established on reliable grounds. T. G. M.

WOUND INFECTIONS. By COLONEL SIR ALMROCH E. WRIGHT, M.D., F.R.S., Consulting Physician to the Expeditionary Force. Pp. 96; 12 illustrations. New York: William Wood & Co.

THIS little work takes up the all-important question of how to handle wound infections, the data and experiments having their being in connection with the present war. Two chapters are devoted to the biological evolution of wound infections and the experimental investigation of white blood corpuscle emigration into wounds.

Treatment is outlined under three heads: (1) by antiseptics; (2) by physiological methods; (3) by vaccine methods.

In an epilogue the author makes a strong plea for a more systematic routine in the experimentation, treatment and publication of results of wound infections.

The book makes very instructive and interesting reading.

E. L. E.

INFANT FEEDING. By LAWRENCE T. ROYSTER, M.D., Attending Physician, Bonney Home for Girls; Physician-in-charge, King's Daughters Visiting-Nurse Clinic for Sick Babies, etc. Pp. 144; 3 illustrations; 2 charts. St. Louis: C. V. Mosby Company, 1916.

THE purpose of this book, as expressed by the author, is to furnish the essentials, and only the essentials of infant feeding in a compact and succinct form, for the busy practitioner. He realizes that the book contains many imperfections, but hopes that its purposes will be taken into consideration. He thus disarms criticism of its inadequateness as a text-book on infant feeding. The reviewer cannot refrain from the comment that the practitioner who is too busy to read more than a work like this on such an important and complicated subject as infant feeding, would do well to relinquish that part of his pediatric practice to those who can give it the time it deserves. J. C. G.

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MEDICINE

UNDER THE CHARGE OF
W. S. THAYER, M.D.,
PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,
AND
ROGER S. MORRIS, M.D.,
FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

A Study of an Epidemic of Trichinosis with Cures by Serum Therapy.—B. F. SALZER (*Jour. Am. Med. Assn.*, 1916, lxvii, 579) makes a preliminary report of his clinical and experimental studies on trichinosis. Most of his findings are new and many of them are of such importance, if confirmed, that the author's summary of his findings is given practically in his own words. The Kernig reaction was present in all of fourteen human cases. The reflexes in the lower extremities were abolished in all the cases and are still absent (six months). Trichinæ were found in the blood in nine of the 14 cases and in the cerebrospinal fluid in 8 cases. These and other less important points have been demonstrated previously and are confirmed by the author. His newer clinical and experimental results are chiefly as follows: The diazo reaction was in direct proportion to the degree of eosinophlilia. The leukocytosis diminished as the eosinophilia increased. The blood coagulation time was markedly prolonged. In a child three months old trichinæ were still present in the cerebrospinal fluid three months after clinical recovery. In one case trichinæ were found in a pleural exudate and the disease was reproduced by injecting this fluid; they were not found in the urine of any of the fourteen patients. Trichinæ were not found in the uterus but they were abundant in the placenta. The embryos were present in large numbers in the milk of a nursing woman, and were also present in a piece of excised mammary gland. In one case complicated by furunculosis, trichinæ were found in the pus of a furuncle of the external auditory canal. On inoculation of the pus into a rabbit, trichinosis were produced. The feces were clay-colored throughout the disease in every case. This color, the author believes, is due to reduction of the bilirubin by living trichinæ, whose presence in great numbers was demonstrated in one case by means of the duodenal tube. Trichinæ were present in the stools of all the cases throughout the disease. They were proved to be present by making the stools alkaline and allowing them to stand twelve to twenty-four hours. In experimental trichinosis, embryos were not found in the blood during the first five days. On the seventh day two or three were observed in every field. Trinchinæ were absent in the heart muscle. The use of serum from human patients who had recovered removed the eosinophilia persisting after recovery in man or animals within forty-eight hours. The injection of normal serum had no therapeutic value in man or animals, and the same was found true of salvarsanized serum and salt solution. In animals the injection of convalescent serum gives an almost complete prophylactic result. Animals fed with infected meat within twenty-four hours after the administration of the serum may develop a mild form of trichinosis. Animals fed at a period later than that prove to be immune. If immune serum is mixed with infected meat and then fed the animals do not develop trichinosis, although the injestion of the same meat without the serum is invariably followed by the disease. In 2 cases of trichinosis in the very active stage of the disease the use of immune serum proved to be of remarkable curative value. There was a decided drop in the temperature within six hours and the abnormal temperature was entirely gone within forty-eight hours. The eosinophilia showed a considereble drop within six hours; there was then a secondary rise and then a return to the figures found in normal blood within forty-eight hours. In twenty-four rabbits suffering from the disease experimentally produced the immune serum had a curative effect within twenty-four hours.

The Quantitative Determination of Amylase in Blood Serum and Urine as an Aid to Diagnosis.—P. Stocks (*Quart. Jour. Med.*, 1916, ix, 216) employed modifications of Wohlgemuth's method for determination of amylase and has made a special study of pancreatic disease to determine whether diagnostic aid might be secured by this means. He was lead to undertake the study because of the frequency with which cancer of the stomach and liver is found to be primary in the pancreas. The author gives in detail the technic of the method, together with observations on individuals with presumably normal amylase values. His application of the tests to patients with pancreatic and other diseases has led him to the following conclusions: Amylolytic ferment is present in the blood serum and urine of all healthy individuals, and has also been found in all the body fluids examined. The level is practically constant in the blood serum; the level in the urine is subject to diurnal variations due chiefly to the digestive functions. The ferment is of pancreatic origin and is absorbed directly by the blood. No proof of the action of anti-amylase has been found. Disease of the kidneys causing any diminished permeability of these organs reduces the amount of ferment in the urine, and consequently raises the amount in the blood. Any disturbance in the ratio D (blood): D and M (urine) indicates renal insufficiency. Severe passive congestion also raises the amount of amylase in the blood. With these exceptions, any increase of the ferment in the blood serum denotes pancreatic mischief. The values have been found raised in all cases of pancreatic disease, the increase depending on the degree of obstruction in any part of the gland or its ducts, and on the acuteness of the condition. The highest values were found in a case of acute pancreatitis. The estimation of the amylolytic capacity of the blood serum and the urine is a most delicate test of the efficiency of the pancreas, and consequently is a most delicate and reliable test for disease of the pancreas, the author states. The use of the simplified modification of Wohlgemuth's method, and the use of an identical technic for serum and urine are justified, he believes, by the consistency and regularity of the results obtained.

Carbon-monoxide Poisoning.—Y. HENDERSON (*Jour. Am. Med. Assn.*, 1916, lxvii, 580) gives a resumé of his observations on carbon monoxide poisoning. Many of the facts he mentions are, as he says the discoveries of Haldane, whose work is not sufficiently well known to practitioners. The author's summary is as follows: Carbon monoxide is a physiologically inert gas, except in its affinity for hemoglobin. Its toxic effects are wholly due to the inability of the blood combined with carbon monoxide to transport oxygen to the tissues. A permanent compound with hemoglobin is, however, not formed. In the presence of excess of oxygen, or even of pure air, carbon monoxide is rapidly given off and the oxygen carrying power of the blood is restored. The continuance of coma, the subsequent tissue degenerations, and death after several days, resulting from carbon monoxide poisoning, are not due to retention of the gas, but are the results of injury to the brain and other organs by the insufficiency of oxygen supplied to them by the blood while the patient was breathing the gas. There is no reason to believe that either bleeding or transfusion of blood is beneficial. They are more likey to be harmful. Fresh air—with oxygen inhalation as early as possible (within one-half hour)—symptomatic treatment, and good nursing are the only measures to be recommended. Practically the die is cast for death, permanent defects, or complete recovery at the moment when the patient is brought out of the asphyxial atmosphere. It is just possible theoretically that alkali therapy may be beneficial in combating the acidosis induced by asphyxia.

The Treatment of Arthritis by the Intravenous Injection of Foreign Protein.—J. L. MILLER and F. B. LUSK (*Jour. Am. Med. Assn.*, 1916, lxvi, 1756) refer to the work of Kraus and of Lüdke, which showed that typhoid fever may be treated apparently as successfully with intravenous administration of colon bacillus vaccine as with typhoid vaccine. Lüdke later found that he could obtain similar results with a solution of proteose prepared by Drs. Jobling and Peterson. The authors then decided to apply this method of treatment to acute, subacute and chronic arthritides. As their supply of proteose was limited and as they believed the reaction was due solely to the foreign protein, they substituted a typhoid vaccine for the proteose. The bacilli from the Rawling's strain were killed by heating to 55° C. and were preserved by the addition of 0.5 per cent. phenol. In the preliminary cases a dose of 150,000,000 was given intravenously. "The reaction was the same as when the vaccine was given to a typhoid patient, except that the leukocytosis was much more marked, in two instanecs reaching

52,000. Immediately following the injection there was a moderate leukocytosis which increased slightly until the chill, which usually occurred in from five minutes to one hour. During or immediately following the chill, there was a rapid drop in the leukocytic curve resulting either in a normal count or a leukopenia, followed promptly by a rapidly developing leukocytosis, which reached its maximum usually at the end of four and occasionally at the end of twelve hours, gradually returning to normal in from twenty-four to forty-eight hours." Following the chill there was a profuse sweat lasting several hours. In three patients with acute arthritis there was a second chill which came on six to seven hours after the intravenous injection. A temperature of 105° was not unusual in the acute arthritides. Nausea and headache were practically always complained of after the chill. In three of ten cases of acute articular rheumatism, immediately following the intravenous injection of 150,000,000 killed typhoid bacilli, the fever terminated by crisis, the joint tenderness began to disappear, and within from twelve to twenty-four hours the joints were apparently normal. In these three cases the results were permanent. All of the seven remaining cases were very much benefited following a single injection, but the results were either not permanent or soreness remained in the affected joints. Three or four injections, however, sufficed to relieve all symptoms. Relapses nevertheless were frequent. The authors are now giving daily injections until four or five have been given in order to see if relapses can be avoided. Results quite as satisfactory were obtained in six cases of subacute arthritis of from three to nine months' duration. After three or four injections the patient could move his joints with comfort. Even better results were secured in cases of chronic gonorrheal arthritis of from two months' to three years' duration. All of seven cases showed decided benefit. The results appeared to be less satisfactory in two patients with acute gonorrheal arthritis. Complications in the joint cases such as endocarditis or pericarditis, seemed to be unaffected by the treatment. In gonorrheal arthritis, in fact, the urethral discharge was temporarily increased following the injection of vaccine. The treatment, the authors believe, deserves further trial. It is obvious that foci of infection, when found, should receive the usual treatment.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Localization and Extraction of Projectiles and Shell Fragments.—Flint (*Ann. Surg.*, 1916, lxiv, 151), writing from his experience in a

French military hospital, says that there have been great differences of opinion expressed by military surgeons concerning the advisability of extracting or leaving projectiles or shell fragments either before or after they are healed in the tissues. He gives the following indications for extraction: (1) Instances where the projectile or fragment forms a focus of suppuration which will probably continue until either the fragment is removed or until it is discharged spontaneously from a fistula. (2) Instances where the foreign body is causing pain. This may be situated either in the muscles, near the bones or nerves, in tendons or even superficially. Not infrequently the pain may be due to the cicatrix surrounding the fragment rather than the fragment itself. (3) Instances where the wounds of entrance or exit have healed, leaving the projectile in the tissues surrounded by a small abscess or focus of infection encapsulated from the surrounding tissues. (4) Any interference with the function of the tissues or organs forms a rational indication for a removal of the offending foreign body. (5) Instances where the presence of the foreign body may influence the mental condition of a patient to a degree which justifies its removal. (6) Another group of cases which are of great importance in military surgery belong to the malingering type, who complain that shell fragments are painful in order to avoid the responsibility of further military service Such instances require removal in order to restore the wounded man to military service. (7) Cases where a lead projectile may give rise to lead poisoning. (8) When cases are brought in fresh from the front and operations are performed for infections, better drainage, removal of loose bone fragments in compound fractures, etc., the projectiles should be removed if possible. The contraindications may be briefly summarized as follows: (1) No operation should be performed which does more injury to the tissues than the presence of the foreign body. (2) The operations should not be performed in clean cases where there is not a reasonable expectation of aseptic healing or a great probability of finding the projectile. The methods for the localization of the foreign body must be suited to the requirements of the individual case. Radiography was not satisfactory. Up to the present time the vibrating magnet and the Sutton cannula with the harpoon are perhaps best adapted for immediate operation on cases fresh from the front, although their limitation must be constantly borne in mind. The profundometer of Irvin is by all odds the most useful and the most general in its application, and provides localization data upon which practically any extractor can be made.

Observations on the Diagnosis and Treatment of Trifacial Neuralgia.—Beckman (*Ann. Surg.*, 1916, lxiv, 242) studied 177 cases of trifacial neuralgia which came under his observation. A mistaken diagnosis is not often made by those who have seen a number of cases, A continuous aching pain or pain that throbs with the pulse is not trifacial neuralgia. The pain is very often started by the slightest irritation of a certain localized area on the face or tongue, and occasionally by the irritation of a single tooth, "doloro genetic zones" or "trigger zones." Beckman's cases have not appeared to be more neurotic than the average. An excision or evulsion of the peripheral nerve branches was done in 19 cases. The longest period of relief in any of the series was two years. In this patient the infraorbital nerve was evulsed and a screw placed in the foramen. Only five of the patients were relieved for one year or longer. The average time of relief was 8.4 months. In 146 patients the method of Levy and Baudoin was employed for injecting the main nerve branches at the base of the skull with alcohol. Letters have been returned from 120. The plan has been followed by injecting the second and third divisions of the nerve when one of them was involved. Occasionally some bleeding resulted, which produced considerable tension underneath the temporal fascia. In three patients, there was inflammatory reaction of the cornea which cleared up within a few days; in two there was temporary paraysis of the external rectus muscle of the eye, and in six, stiffness of the muscles of mastication, which gradually subsided. The latter were patients who had had several injections. In one instance the relief lasted five and one-half years, in another three years, and still another three and one-half years. However, only 30 were relieved for one year or longer. The average length of time for the whole series of 120 from whom letters were received was 9.4 months, a slightly longer average than the time of relief following the series of operations on the peripheral branches. Relief of pain for six months or less occurred in 77 of the 120 (64 per cent.). Beckman has had no experience with injections into the Gasserian ganglion, and thinks that if this method becomes generally adopted there will be many serious complications. Eighteen patients have had operations on the Gasserian ganglion. Eleven patients had the ganglion removed after the Hartley-Krause method, 1 was operated on by the method of Abbe, and 6 by the method of Frazier. Thirteen of the living patients have been completely relieved of their pain or the recurrences have been so slight that they consider their condition satisfactory. The remaining 3 patients have had recurrences, probably from incomplete operations. There were two operative deaths in this series. Beckman believes that the same number of patients operated on today would give approximately 100 per cent. permanent relief from pain. At the present time evulsing the posterior nerve root or removing the ganglion entirely is the only operation insuring permanent relief, and the mortality is no higher than that of many serious operations performed daily by surgeons throughout the country. It should be the operation of choice for a person in reasonably good physical condition.

More Radical Treatment of Duodenal and Gastric Ulcer.—Deaver (*Ann. Surg.*, 1916, lxiv, 294) says that where the ulcer is small and is located upon the anterior wall of the first portion of the duodenum it is his practice to exercise it, close the opening in the intestine, plicate the duodenum and make a posterior gastro-enterostomy. When an ulcer in this portion of the intestine is large, but extends short of the head of the pancreas, he amputates the duodenum below the lesion, purse strings it, inverts, excises the pylorus, and makes a posterior gastro-enterostomy. When the ulcer is on the posterior wall of the first portion of the duodenum and not too adherent to the posterior abdominal wall to permit of freeing the duodenum, he practises the same technic as in large ulcers upon the anterior wall. In acute perforation of a duodenal ulcer he makes a posterior gastro-enterostomy at the primary operation. He has now operated on 44 patients in this manner with but one death. He always treats the chronic indurated ulcer of the pylorus by doing a pylorectomy. When the induration of such an ulcer involves the lesser curvature in proximity to the pylorus, he does a subtotal gastrectomy. Posterior gastro-enterostomy does the greatest good when the pylorus is obstructed. In ulcers located other than at the pylorus does but little if any good. That this operation does any good by drainage alone, he thinks doubtful. It does most good when there is pyloric obstruction and when the ulcer is excised. When excision of the ulcer has not materially interfered with the mechanics of the stomach, with the exception of the pyloric ulcer, posterior gastro-enterostomy should not be done. To summarize, he has come to the conclusion that all ulcers of the duodenum or stomach are best treated by excision.

Observations on the Occurrence of Syphilis in the University of Michigan Obstetric and Gynecologic Clinic.—PETERSON (*Surg., Gynec. and Obst.*, 1916, xiii, 280) says that for the past year there has been a hospital rule that every in-patient should have a Wassermann taken, and the rule has been fairly well carried out. In 2000 patients there were 110 distinctly positive Wassermanns in which the diagnosis in almost every case was confirmed by the department of syphilology. Among the doubtful reactions there were 8 in which the patients were afterward proved to be syphilitic. This shows that 6 per cent. of the general run of hospital patients are syphilitic. Wassermann reactions should be taken routinely, especially where even careful histories fail to arouse suspicion of latent syphilis. The percentage of lues in 381 cases in the University Maternity was 4.7 as shown by the Wassermann reactions and expert physical examinations. In 18 cases of syphilis among the number examined only 8 gave a history of lues. In only the same number (8) were there positive physical signs of lues. As shown by the histories of the 18 cases there is a greater chance for the syphilitic mother treated by salvarsan and mercury to give birth to a living, full term child than where no treatment is given during pregnancy. The newborn infants of the mothers so treated do not give positive reactions, although undoubtedly they are syphilitic and later probably will show signs of the disease. A certain proportion of the newborn children of untreated syphilitic mothers will give positive Wassermanns. Out of 390 gynecologic patients subjected to the Wassermann test, 22, or 5.6 per cent., gave positive reactions. In only 5 of the 22 luetic patients was there a history of syphilis. Hence the importance of such examinations, or a serious general disease will be overlooked and the gynecologic patient will remain uncured.

The Transplantation of the Articular End of Bone Including the Epiphyseal Cartilage Line.—HAAS (*Surg., Gynec. and Obst.*, 1916, xxiii, 301) says that from his experiments and the results in general on transplanted bone the following conclusion is offered regarding the fate of bone after transplantation. Although each part of transplanted bone possesses the power to regenerate independently and without the aid of neighboring bone, this autonomous newly formed tissue does not possess that property which is necessary for a continued existence, and it will ultimately entirely disappear. Some additional stimulus is needed and such conditions are only obtained when the transplant is in direct contact with normal growing bone. Therefore, when there is failure of such connection the transplanted bone at first shows evidence of regeneration but if a sufficient time is allowed to elapse, it will ultimately entirely disappear. However, if it is united with the cut surface of normal bone it will continue to live because certain necessary additional stimuli and new elements will be supplied by the host. It is possible that certain chemical or physiological stimuli are supplied by the living intact bone, after which the regenerated bone on account of these additional factors is able to persist permanently. Undoubtedly some definite osseous elements from the bone of the host invade the transplant and either replace the temporary bone or give to it certain requisites for its perpetuation. Although function may play a factor in the development of bone it is not of prime importance in determining the permanency of that tissue.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

Specific Treatment of Infantile Paralysis.—Sophian (*Jour. Am. Med. Assn.*, 1916, lxvii, 426) writes concerning his experience regarding treatment in the present epidemic of infantile paralysis in New York City. He divides the treatment into: (1) relief of hydrocephalus; (2) intraspinal injection of serum; normal serum, horse serum or convalescent; (3) relief of special symptoms, as respiratory paralysis; (4) symptomatic general treatment, and (5) orthopedic treatment. Hydrocephalus with its pressure symptoms is most pronounced during the acute stage. In most cases it is only moderate, but not infrequently, especially in the cerebral cases, it is quite pronounced. In the latter the patients are often very stuporous, with twitchings, convulsions and respiratory embarrassment. Paralysis of the respiratory centre is the usual cause of death in infantile paralysis. Early relief of respiratory embarrassment is therefore important. One lumbar puncture usually suffices, but in some cases it must be done several times till relief is permanent. So far a highly immune serum for poliomyelitis has not been obtained. Sophian believes that the production of a hyperleukocytosis in the cerebrospinal fluid has a very distinct therapeutic value in the treatment of epidemic poliomyelitis. Such a hyperleukocytosis can be induced by intraspinal injections of normal horse serum or human serum. The objection to horse serum seems to be the sensitization to foreign protein; therefore, normal human serum would be preferable. In order to be of most value, the serum should be used very early in the disease, during the acute inflammatory stage, if possible in the preparalytic stage, especially if prevention of paralysis and abortion of the disease is to be looked for. The use of a blood serum obtained from cases convalescent from poliomyelitis offers the advantage of a human serum plus the presence of immune bodies. That serum obtained from at least recently convalescent cases contains immune bodies has been proven by the neutralization test in the monkey. Netter reported the use of convalescent serum in thirty-two cases, with excellent results. With regard to the effects produced by the intraspinal injection of various forms of serum, Sophian states that in a series of cases treated by convalescent serum, the results were certainy no better than in those treated by normal horse serum. In the normal horse serum series, two cases treated in the preparalytic stage were aborted and one case was aborted under the convalescent serum treatment. The best results were obtained in early cases but some of the late cases treated showed more improvement than is generally seen in untreated cases. There was more rapid convalescence and improvement in the paralytic condition. Sophian has had very little experience with the local administration of epinephrin. Respiratory paralysis is the most common cause of death in infantile paralysis. It is therefore of prime importance to meet this complication early, so as to tide the patient over the critical period until congestion and inflammation about the respiratory centre subside. In comatose patients, the pharyngeal respiratory apparatus has been suggested by Meltzer and for conscious patients, if possible early after respiratory difficulty has set in, the administration of oxygen under pressure by the method of Meltzer may be of value. General treatment is very important as the patients are frequently helpless and require especial care as to feeding and care of bowels and bladder. Orthopedic treatment should be begun as early as possible after the acute symptoms subside.

The Treatment of Tuberculosis with Cyanocuprol.—Otani (*Jour. Exper. Med.*, 1916, xxiv, 187) reports the results of treatment in eighteen cases of tuberculosis, in a numbr of which very favorable results were obtained, although in some absolute failure was noted. He believes that cyanocuprol is markedly effective in tuberculosis and that it will play an important part in clinical medicine. It may be used more generally than tuberculin. The amount of the dose is closely related to the reaction and the final results. It should be determined for each patient after a careful examination of his symptoms. The maximum dose of 8.5 c.c. should in no case be exceeded. The shortest interval between injections should be two weeks. If the drug is given after a shorter interval, no improvement is observed and the effects are sometimes dangerous. In order to obtain the best results the patient should be placed under conditions of complete physical and mental rest after the injection; this applies even to light cases. During the period of the treatment irritants to the lesion, such as potassium iodide or tuberculin, should be avoided; apricot juice, guaiacol and its derivatives and iodol are contraindicated. No marked idiosyncrasy has been noted and no accumulative effects have been observed.

Metabolism Studies Before and After Splenectomy in Case of a Pernicious Anemia.—Pepper and Austin (*Arch. Int. Med.*, 1916, xviii, 131) report metabolism studies in a case of pernicious anemia before and after a splenectomy which was performed for therapeutic effect. The patient was an adult with pernicious anemia of a moderately hemolytic type in whom the splenectomy was followed by the disappearance of the discoloration of the skin and by prompt and persistent improvements in the condition of the blood and general health. Metabolism studies before and after splenectomy gave the following results: A slight positive nitrogen balance before splenectomy was followed by an increased nitrogen retention fourteen days after operation and a return to the preoperative balance after one month. The output of uric acid, although never exceeding normal limits, showed a decrease of 22 per cent. after operation. The output of iron through the feces, although never above normal, showed a decrease of 40 per cent. after operation. The excretion of urobilinogen and urobilin in the feces before splenectomy was about three times the normal; two months after operation the output was about one-seventh of that before splenectomy.

Results Obtained in the Treatment of Diabetes Mellitus.—Joslin (*Bost. Med. and Surg. Jour.*, 1916, clxxv, 147) says that during the year ending May 1, 1915, 211 cases of diabetes came under his observation, and of this number 31, or 15 per cent., died; during the subsequent year 314 cases were seen and 37, or 11.7 per cent., have died. These figures represent a decrease in mortality over the previous year of about 20 per cent. Joslin says these figures are encouraging, but they become still more so when it is considered that a study of the 37 fatal cases seen this last year shows that death might have been deferred in about one-half of these if the methods of treatment now in general use had been adopted. The author states that in a study of the causes of death of 408 cases of his series, it was found that two out of every three (66 per cent.) died of coma, that 87 per cent. of all these who succumbed during the first year of the disease died of coma, and that this was the case in 100 per cent. of the fatal cases in children. Therefore, if the mortality of diabetes is to be reduced, our energies should be directed first toward the avoidance of coma, because the treatment of coma is so unsatisfactory; and second, particular attention should be exercised in the management of cases of diabetes in the first year following the disease. Furthermore, all cases should be persistently followed up, and the good effects of treatment not be allowed to lapse by indifference or neglect.

The Rate of Absorption of Various Digitalis Preparations from the Gastro-Intestinal Tract.—Haskell, McCants, and Gardner (*Arch. Int. Med.*, 1916, xviii, 235) found that the infusion of digitalis seems to be absorbed more slowly than the tincture in animal experiments that they conducted. They also tested some of the special digitalis preparations which have been claimed to possess a more rapid rate of absorption from the gastro-intestinal tract than official digitalis preparations. The three special preparations of digitalis, namely, digipuratum, digalen, and digipoten, seem to possess no decided advantage over the official tincture. Their chief practical disadvantage is their high comparative cost. Digipuratum in their experiments seemed to be absorbed less rapidly than was the tincture. The sample of digipurratum tested was somewhat stronger than the official tincture, but this did not nearly compensate for the difference in absorption. Digalen was absorbed more rapidly but the variability in strength and the low standard of strength (only about one-fourth the physiological activity of the tincture), together with the relatively high cost of this preparation, more than offset this possible advantage.

The Treatment of Amebic Dysentery.—BATES (*Jour. Am. Med. Assn.*, 1916, lxvii, 345) says that one of the first and most necessary factors in treatment, whether the case is mild or severe, is complete rest. The patient is put to bed and given a saline purge or castor oil. He is kept in bed until all the acute symptoms have subsided. After the purgative has acted, emetin or ipecac is begun. Bates advises one-half grain injections of emetin daily for an adult until two grains are given. The dose is then increased to one grain a day and continued until all amebæ disappear from the stool. This will usually require a total of from five to six grains of emetin. At this time the emetin is discontinued and bismuth subnitrate in large doses is begun. Bismuth acts in two ways: (1) as a sedative on the intestinal tract and as an aid toward the healing of the ulcers present; (2) as was first pointed out by Deeks, bismuth itself acts as an amebicide and is an added help in destroying such amebæ as may be left or those that may be formed from the "encysted stage." Bismuth is usually given in one dram doses every four hours until the stools are well formed, and until some constipation is present. It may then be reduced to one dram, three times a day until the patient is discharged as well. Enemas of normal saline solution, 2 or 3 quarts at a time, are begun as soon as the effect of the salts or castor oil has subsided, and are used every four hours during the waking hours, and continued in this quantity throughout the entire period of the administration of ipecac or emetin. They may then be reduced to two or three a day and later to one a day, merely to prevent the constipation following the bismuth. Experience has shown that sweet milk is the best food in amebic dysentery. It may be given every two hours during the day in quantities of from 4 to 8 ounces at each feeding. After the more acute symptoms have passed and the stools are beginning to be formed, the milk may be gradually increased in amount and the intervals between feedings lengthened. Soft-boiled or poached eggs may be added to the diet with one slice of dry toast at each feeding. To carry out this treatment until one is reasonably sure that all ulcers are healed will require in the acute cases at least four weeks time and in the more severe cases from six to eight weeks. Bates is confident that the treatment just outlined will effect a cure of amebic dysentery in a large majority of cases. Nevertheless it must be expected, especially in the tropics, that some cases will be encountered so far advanced that no treatment can be of help. Occasionally relapses will occur in spite of the treatment outlined. In cases when two or three efforts at treatment by medicinal means have failed, appendicostomy will have to be advised. After this the colon should be flushed out several times a day with saline solution, followed by powdered ipecac suspended in some bland material, such as mucilage acacia.

Dietary Deficiency as the Etiological Factor in Pellagra.—Vedder (*Arch. Int. Med.*, 1916, xviii, 137) in his conclusions states that there is a certain similarity between pellagra and other known deficiency diseases, namely, beriberi and scurvy. Much of the evidence that has been presented as a proof of the infectious nature of pellagra can be reasonably explained in accordance with a deficiency hypothesis. A deficiency is demonstrable in the diets of most pellagrins. This deficiency appears to result from the too exclusive use of wheat flour, in association with cornmeal, salt meats and canned goods, foods that are known to be deficient in vitamins. Changes in the diet of the people of the South have occurred during the past ten or fifteen years. Since all the changes that have occurred are not known and they cannot judge accurately the importance of the known changes, it is unscientific to assume that the recent increase in pellagra cannot be due to such changes. The hypothesis that pellagra is caused by a deficiency is very plausible and must be taken into consideration in subsequent studies of this disease.

Hay Fever. Its Treatment with Autogenous Vaccines and Pollen Extract.—Medalia (*Bost. Med. and Surg. Jour.*, 1916, clxxv, 201) says that the bacteria found in the secretions of the nose and eyes of hay fever patients previous to their attacks and during their supposedly healthy condition are markedly suggestive of the important role played by such bacteria and their products. They are, he believes, the determining factor between individuals being susceptible to hay fever or not, since they may be, in a measure, responsible for the breaking up of the pollen, setting free the albumens and thus causing pollenosis. The bacterial infection, though secondary to pollenosis, is apparently responsible for the difference between pollenosis, producing a mere transient sneezing, or true hay fever attacks with all their accompanying symptoms. The good results obtained by the use of autogenous vaccines, as reported in the literature and his personal results, suggest to the author the important relation of bacteria to this disease. He reports six cases treated with a combination of autogenous vaccines and pollen extracts, all resulting in "seasonal cures." The results in these cases have been so decidedly beneficial that he believes the conclusion is justified—that the autogenous vaccine has yielded better results in the treatment of these hay fever patients than any other therapeutic procedure thus far suggested in the treatment of this disease.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND FREDERICK O. WAAGÉ, M.D.,
OF PHILADELPHIA.

Care and Feeding during the First Month.—Pisek (*Arch. Pediat.*, 1916, xxxiii, No. 6) states that in spite of marked decrease in the infantile mortality, that of the first month of life is still woefully too high, and can be lowered only by active measures of prevention and correction. In spite of the well-known fact that babies thrive so much better on breast than on cow's milk, and that 85 per cent. of all infantile deaths are among those artificially fed, many are still removed from the mother's breast for insufficient reasons by the physician or nurse. Their decision is often based on the fact that no milk has appeared in forty-eight or seventy-two hours, or upon one hasty or inaccurate examination of the milk, or because of vomiting or an occasional abnormal stool. Every effort should be made to enable the baby to have the breast alone, or at least part breast feeding during this first month of life, for, while it will apparently do well for ten days or two weeks on a formula, its resistance then breaks down and its digestion becomes sadly disturbed and is hard to correct. Even a small amount of breast milk aids in the digestion of the cow's milk. If artificial food must also be supplied it should be a weak formula, low in fats and proteins, although high in sugar. An amount of food necessary to produce a gain in weight need not be given, or, in other words, the caloric requirements are not to be fulfilled until the end of the second week is reached. The three-hour interval is preferable, for, although the newborn infant can be trained to take the breast at four-hour intervals, it is not a natural interval, and unless vigorous, he is apt to need, in addition, artificial food. Weighing before and after a nursing throughout at least one whole day is essential in questionable cases to determine just how many ounces he is receiving. The author's experiments with the Roentgen-rays on infants' stomachs proved conclusively that babies can take an amount far in excess of their rated gastric capacity, because the milk tended to pass at once into the duodenum.

Acute Poliomyelitis: The Clinical Types of the Disease.—Koplik (*Arch. Pediat.*, 1916, xxxiii, No. 8) says that poliomyelitis is primarily an epidemic disease, and as a sporadic condition has attracted very little notice. The sporadic cases do not differ clinically from the epidemic type of the disease. An attempt to connect this disease with the occurrence of cases of cerebrospinal meningitis, has broken down to give place to the feeling that poliomyelitis is an entity, clinically occurring in epidemics in the late spring to late autumn. We owe much of our clinical knowledge of the disease to Media, who described the clinical types of acute epidemic poliomyelitis in 1884, much to the astonishment of most pediastrists, who still retained the simple picture as portrayed in older text-books of poliomyelitis anterior, as a simple infantile paralysis. This old conception of poliomyelitis, which without prodromata, was followed by an overnight paralysis of one or more extremities, has been lost sight of in the more thorough modern clinical analysis of the symptomatology of the disease, and we can now describe the following types: (1) The abortive; (2) the bulbospinal; (3) the cerebral and meningeal; (4) the bulbopontine. These types may be easily understood if we conceive poliomyelitis to be an acute infectious disease, and to the extent to which the infection goes, to that extent do we obtain a symptomatology, so that the old descriptions of the disease as an involvement of the ganglion cells of the anterior bones of the spinal cord must today be looked on as a small fractional part of the story. The abortive is probably from a scientific epidemiological standpoint the most important type of the disease, for it is through these cases that the disease is spread to others. It is the type which does not go into paralysis, and with recovery leaves the patient uninjured as to the muscular motor apparatus. In an epidemic, fever, headache, vomiting, slight rigidity of the neck, increased or diminished reflexes at the knee must be carefully observed for further development. Aside from an epidemic few would give such symptoms a place other than among the extremely indefinite signs of an affection. The meningitic and cerebral types should be combined, because of the cerebral symptoms which give rise to a picture closely simulating meningitis. The meningeal form runs its course with cerebral symptoms due to a real injection of the meninges of the brain and cord. The bulbar or pontine type of the disease is another form which has only been recognized lately and deserves notice as a distinct form of poliomyelitis.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Acidosis Complicating Pregnancy.—Ely and Lindeman (*Am. Jour. Obst.*, July, 1916) report the case of a multipara who in her first pregnancy had great disturbance of digestion without definite symptoms of nephritis, but with acetone and diacetic acid in the urine. Labor was normal, but the child suffered from vomiting and disturbance of digestion. During the second pregnancy acetone and diacetic acid were present at the second month, and vomiting occurred. Rapid loss of weight followed. Use of alkalis and irrigation of the colon produced no effect. Rectal feeding did little good. Pulse and temperature continued normal, but the patient became profoundly toxemic. In the thirteenth week of pregnancy the uterus was emptied. This had no effect upon the vomiting. Analyses of the blood were then made, and direct transfusion was practised, taking the blood of the husband of the patient. This was done after the blood of twelve other persons had been examined to find one most suitable. For twenty-four hours before transfusion the donor was given large doses of bicarbonate of sodium; the effect upon the patient was surprising. At 12.30 P.M. 400 c.c. of blood was taken from the patient and 1100 c.c. transfused from the donor, with 300 c.c. of Lock's solution. Beginning two hours after transfusion the patient was given predigested food every two hours, with soda solution in the bowel every four hours. The patient vomited but three times in the next twenty-four hours, and after that was able to take diet and preparation of iron. A second transfusion from the same donor was given, using a smaller quantity, and the patient went on to uninterrupted recovery. Before the transfusion the percentage of urea in the blood was low, and this increased decidedly after the transfusion. Blood ammonia was undoubtedly high before transfusion, for three days after it was more than twice the normal. It is interesting to note that the carbon dioxide of the blood plasma was 55 per cent. before transfusion, and that after transfusion this rose to 94 per cent. This valuable report should draw attention to the importance of acidosis in the toxemia of pregnancy. It will be observed that there was no evidence of kidney involvement, that emptying the uterus did no good, and that the only efficient measure consisted in correcting the condition of the blood. Transfusion by the syringe method is comparatively simple and safe. If the possibilities of acidosis should be kept in mind in all cases of toxemia, a prompt diagnosis and efficient treatment after the method employed by these writers should be tried.

Labor following Ventral Suspension.—Caldwell (*Am. Jour. Obst.*, July, 1916) reports three cases of labor complicated by ventral suspension in which serious conditions developed. The first patient was a multipara who had a curetting, repair of the perineum, and ventral suspension of the uterus. The following pregnancy had preceded normally, but at its close it was found that the fetus was in transverse position and that this could not be corrected by external manipulation. The patient was admitted to Bellevue Hospital with slight pain. On examination the cervix was high, and pointing directly backward and toward the promontory. It was partially softened and admitted two fingers. No presenting part could be made out. Six hours after admission the membranes ruptured, the uterus was in tonic contraction with a beginning retraction ring. The cervix was high, pointing directly backward toward the promontory, and there was dilatation for three fingers. Under anesthesia the head and a foot were found in the lower segment, and a slow podalic version was done; the cord did not pulsate but the patient was allowed tó come out of the anesthesia. A tight binder was applied with the hope that the patient would deliver the fetus in breech presentation. Very slight traction was maintained on the child's foot. Although the cervix completely dilated, and pains were good, there was no advance. The patient was again anesthetized and slow breech extraction performed; the aftercoming head was perforated and delivered. Following the birth of the child there was copious bleeding, and the patient became severely shocked. On removing the placenta by the hand a tear of the cervix on the right side was discovered. A hot intra-uterine douche was given and the cervix and vagina firmly packed, and the patient stimulated, but death occurred in less than two hours without further bleeding. At autopsy very dense fibrous adhesions were found between the anterior surface of the uterus and the abdominal wall. On the right side a tear extended obliquely upward for 12 cm. with bleeding into the right broad ligament. A well-marked retraction ring was still present. The second case was a primipara who had previously an operation removing the right ovary and appendix. A year after she had a second operation for adhesions. A third operation was done to free adhesions. She was admitted to hospital thirty-two weeks pregnant, with the history of almost constant abdominal pain. The abdomen was rigid and tender. The stomach was distended but the intestines were not. The uterus was contracted and adherent to the abdominal wall. The cervix was high above the promontory, directed backward; the external os admitted one finger; the internal was closed; there was a slight discharge; the membranes unruptured. The patient was given morphin, but after fourteen hours the cervix did not dilate and section was performed. On opening the abdomen the adhesions were so dense that an opening was made into the sigmoid; injuries to the intestine were immediately repaired. A dead male child was delivered by section, followed by hysterectomy. The operation was followed by persistent vomiting and distention, with death forty hours after. The third case was a multipara admitted to hospital previously with premature separation of the placenta treated by section, followed by complete recovery. She was next admitted to the hospital in the thirtieth week of her pregnancy, with sharp pain in the abdomen followed by vomiting. The abdomen was relaxed and a seven months' fetus could be felt apparently directly underneath the skin; the cervix was hard and did not dilate. There was bleeding at intervals with foul discharge. On section a sac was found in the abdomen containing a dead macerated fetus in foul-smelling pus and gas. The sac was adherent, gangrenous, and removed with great difficulty. Death followed operation. These interesting cases give added testimony against the operation of ventrosuspension in all women during the child-bearing period. When this condition is complicated by pregnancy delivery by section is invariably the safest procedure. The second point of interest is the difficulties caused by extensive adhesions. The reviewer's experience has led him to consider extensive adhesions complicating pregnancy as one of the most difficult and dangerous complications. In one patient a successful Cesarean section was followed some years later by a second operation for the removal of an ovarian tumor complicating the second pregnancy. This proceeded smoothly; the operation was done in early pregnancy because the tumor had become wedged in the pelvis and its pedicle twisted. A smooth recovery followed this, and a second delivery by abdominal Cesarean section was performed later on. At this last operation extensive adhesions between the remains of the right broad ligament, whence had been taken the tumor, and the uterus were present. The emptying of the uterus caused traction on these adhesions and ruptured a large vein in the right broad ligament. The hemorrhage was alarming, but immediately repaired. During the next few days obstruction of the bowels developed, caused by adhesions between the bowels and the torn broad ligament, and although the abdomen was reopened, the patient did not survive. In a second case who had had a Cesarean section, a second section was necessary, and hysterectomy was requested. Adhesions were so extensive that in closing the broad ligaments and stump, the ureters were occluded by pressure. This was subsequently discovered by catheterizing the ureters; the abdomen reopened; the obstruction removed, and the patient making a complete recovery.

Two Cases of Weak Uterine Scars following Cesarean Section.—Beck (*Am. Jour. Obst.*, July, 1916) reports the case of a patient, aged twenty-seven years, who had been delivered two years previously by

Cesarean section. After twenty-four hours' labor the patient was sent to hospital by a midwife. She was delivered by Cesarean section but had fever during the puerperal period; the woman became infected and opened down to the peritoneum. Six weeks later the patient returned to the clinic with a hernia at the site of the abdominal incision. When pregnancy subsequently developed there was a thinned-out scar on the anterior wall of the uterus through which the fetal parts could be very easily outlined. The patient was within ten days of term, and it was thought best to have her enter the hospital. A second section was performed and the anterior surface of the uterus and omentum were densely adherent to the abdominal wall, and the uterine scar was very much thinned. The uterus was opened through these adhesions, making the operation extraperitoneal. Mother made an uninterrupted recovery and the child was in good condition. The second patient was also aged twenty-seven years, and in a previous pregnancy had eclampsia. At this time she was delivered by Cesarean section, mother and child leaving the hospital on the twenty-fifth day. At the end of the second pregnancy she returned to the hospital in labor, the fetus lying obliquely with the breech in the left iliac fossa and the head in the right upper portion. The cervix was almost dilated and membranes unruptured. Under anesthesia it was impossible to move the head, which was bulging through the thinned-out scar of the previous section. The membranes were ruptured, a foot was brought down, and the child delivered by breech extraction. During the delivery the lateral mobility of the head was restricted until the breech had descended far enough to allow the head to be pushed out of the bulging portion of the uterus.

The Puerperal Period Complicated by Sarcoma of the Ovary.—Brodhead (*Am. Jour. Obst.*, July, 1916) reports the case of a negress, eighteen years old, who came to the hospital when pregnant and had a normal delivery with living child. The third day after delivery the temperature rose to 102.5° with rapid pulse, and the patient complained of pain and tenderness, with rigidity in the right inguinal and lumbar regions and in the epigastric and upper umbilical region. The leukocytes were 17,000. On the next day the fever was higher, the tenderness and rigidity increased, and on vaginal examination tenderness was found. Eight days after delivery a mass could be palpated in the right lower quadrant, tender, elastic, and movable, and a diagnosis of abdominal tumor was made. The blood count showed 21,000 leukocytes. On section a sarcoma of the right ovary was found and readily removed, the patient making a good recovery.

The Care of the Perineum after Labor.—Plass (*Johns Hopkins Hosp. Bull.*, 1916) compared the results in two groups of cases. In one the usual routine of antiseptic cleansing was employed. In the other the patient herself used tap water and soap and a wash cloth. In both groups the morbidity was practically the same. In another series of cases in which there had been laceration, and stitches had been taken, better results were obtained without antiseptic irrigation. The wounds healed more satisfactorily and there was a smaller percentage of infection and other complications.

GYNECOLOGY

UNDER THE CHARGE OF
JOHN G. CLARK, M.D.,
PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Escape of Foreign Bodies into the Perineal Cavity through the Uterus in Attempted Criminal Abortion.—Two interesting cases of this character, both of which recovered after operation, are reported by Beckman (*Ann. de gynéc. et d'obst.*, 1916, xlii, 206). The first patient was a young woman, aged twenty-seven years, who had had two previous full-term pregnancies. Having gone somewhat overtime she went to a midwife, who introduced a laminaria tent. Subsequent to this she began to have abdominal pains, followed in a few days by increasing hemorrhage. On admission to the hospital her general condition was good, the abdomen soft, but she was bleeding freely. On examination a silk thread was found issuing from the cervix; this was easily pulled out, but did not bring the tent with it. The cervix was then dilated and the uterus curetted, without finding any foreign body or evidence of perforation. The next day signs of peritonitis became manifest, and the abdomen was opened under general anesthesia. Immediately a large quantity of malodorous pus escaped; the laminaria was found lying among the coils of intestine, which latter were dilated, congested, and in places covered with exudate. There was a quantity of pus and blood in Douglas's pouch. The uterus and adnexa were removed, the vaginal mucosa sutured to the peritoneum, and a gauze drain passed from the pelvis through the vagina, with a second drain through the lower angle of the abdominal incision. After a somewhat stormy convalescence the patient recovered. On examination of the extirpated uterus a perforation large enough to admit a lead pencil was found on the anterior surface just above the peritoneal reflection. The second case was a woman, aged thirty-six years, who had passed through eight normal pregnancies. Her menses failing to appear at the termination of her last lactation she feared another pregnancy, and introduced a bougie 30 cm. in length into her uterus. This was accomplished by placing one knee on a bed beside which she was standing; with one hand she then located the cervix, and with the other introduced the instrument as far as possible, when suddenly it escaped from her grasp and disappeared. She remained quiet the rest of that day, but the next morning began to have pains, and on the fourth day presented herself at the hospital. At this time the abdomen was tender, uterus small, cervix closed, and on examination a foreign body, evidently the bougie, could be felt in the anterior cul-de-sac. Immediate laparotomy disclosed the bougie covered by inflammatory omentum; the intestines were inflamed and lightly adherent. The point of perforation of the uterus was found near the right cornu. The uterus was removed without the adnexa; a drain was placed in the vagina and another in the abdominal wound. Save for slight fever the first few days the convalescence was normal. On examination, no trace of pregnancy was found in the uterus. Beckman thinks that in all cases of this character operation should be performed as soon as the diagnosis is made, and usually by the abdominal route, so that any intestinal injuries may be attended to. He does not think it necessary always to remove the uterus unless this is obviously infected and endangering the patient's life. In other cases, removal of the foreign body and simple suture of the uterine perforation may be entirely sufficient. If the foreign body is encysted in Douglas's pouch posterior colpotomy may be employed in place of laparotomy, the uterus in such cases usually being preserved, though if it is necessary to remove it this may be done by the vaginal route.

Syphilis in its Relation to Gynecology.—The symposium upon this subject which formed an important part of the program of the last meeting of the American Gynecological Society has apparently directed the attention of gynecologists to this heretofore much neglected subject to a very considerable extent. One of the comprehensive papers at this symposium, dealing with the pathologic changes produced by syphilis in the female generative organs, was considered in this department a few months ago. A brief report on the clinical frequency and importance of syphilis as observed in the gynecologic and obstetric services of the University of Michigan was presented by PETERSON (*Surg., Gynec. and Obst.*, 1916, xxiii, 280). The Wassermann test was made upon 390 gynecologic patients, and of these 22 gave sufficiently positive reactions to be judged luetic, amounting to about 5½ per cent. of the total amount examined. While this is possibly a rather low average in comparison to that found in other hospitals over the country, the value of the routine examinations is shown by the fact that only 5 of the 22 positive cases gave a definite history of syphilis, with one additional suggestive history. In Peterson's opinion, the value of these tests cannot be overestimated, since if they are not employed, local conditions may be treated surgically or by other local methods, while the far more important general disease is overlooked. It is undoubtedly true that the diagnosis of syphilis from physical findings alone is far more difficult in women than in men, because the local manifestation are much less marked. Many of the cases that in the past have been puzzles to gynecologists because of their failure to yield to local or surgical measures have undoubtedly been of this type, and will clear up when the true nature of the condition is realized and appropriate therapy instituted. A condition which in the past has been almost completely ignored by gynecologists and obstetricians, which may at times constitute an important element in the symptom-complex presented by their patients, namely *syphilitic fever*, was considered by TAUSSIG (*Surg., Gynec. and Obst.*, 1916, xxiii, 274). He divides this into that occurring as secondary, late secondary, and tertiary syphilitic fever. The secondary precedes or is coincident with the outbreak of the rash. This is believed to occur in about 20 per cent. of all syphilitics, but the rise is not over 1 or 2 degrees and the duration three or four days, so that it often escapes notice. Occasionally, however, the fever is quite high and persistent. Late secondary syphilitic fever is less frequent and more difficult of diagnosis; Taussig reports having seen two cases of this type, both occurring postpartum. In both these women there was persistent high temperature which could not be satisfactorily accounted for, but which disappeared promptly upon the institution of specific treatment. Both patients gave evidences of a syphilitic infection. Tertiary syphilitic fever is still less frequent in occurrence, but is of greater diagnostic importance, since evidences of lues are generally absent and the symptoms may have been forgotten by the patient. The fever is usually continuous, and is attended with an elevation of temperature to 102° or 103°. The cases of this condition of interest to the gynecologist may be subdivided into those in which tertiary syphilis of the genital tract caused the fever, and those in which a gynecologic or obstetric condition was complicated by syphilis in other organs producing fever. Of the former, Taussig has encountered only one definite case, since the gummatous lesions occurring about the external genitals of women and in the rectum apparently do not give rise to this fever. It is the deep-seated lesions, such as those in the liver and osseous system that more often produce it. In several cases of uterine syphilis with extensive gummatous infiltration of the parametrium, however, there was a temperature that could hardly be explained except on the basis of the syphilis, so that the author would class these as suspicious cases of tertiary syphilitic fever. Two instances of the second type are cited; in one of these the lesion was apparently in the liver and spleen, and the other in the bones. In the former salvarsan was given with sudden and complete cessation of the fever and disappearance of the enlargement of the liver and spleen which had been present; in the latter a hysterectomy had been performed, with a secondary laparotomy in an attempt to clear up the cause of the persistent temperature, when the occurrence of pains in the limbs suggested a syphilitic periostitis. Antiluetic treatment resulted in immediate cessation of fever, a gain of eighteen pounds in weight, and disappearance of the bone symptoms.

Regurgitant Menstruation through the Fallopian Tubes.—A rather remarkable example of this condition is reported by Child (*Am. Jour. Obst.*, 1916, lxxiv, 484). The patient was twenty-nine years of age, and had been married for three months. The history, obtained only subsequent to operation, was that in order to prevent conception she had had an "antipregnancy button" inserted in the cervix by a physician, who had instructed her to return to him each month just before the onset of menstruation to have the button removed. This precaution, however, she had neglected, and the button was worn through three periods, during which the flow was scanty, and was accompanied with severe pain, such as she had never had before. The pain became worse and finally continuous, and the button was then removed, but without relief. On examination the pelvis was tender, with fulness in the cul-de-sac. A posterior colpotomy revealed free blood in the peritoneal cavity; upon opening the abdomen the uterus was found to be normal, but the pelvis contained a large amount of thick, dark blood with a few soft clots. Both tubes were normal except for a slight enlargement; their distal ends when drawn up out of the exudate were found to be perfectly free, and the fimbriæ not adherent. From the lumen of both tubes the same dark, sticky blood as filled the pelvis could be squeezed. The canal in each tube seemed to be very much larger than normal, however, as it was possible to introduce a large filiform bougie. The material found in the pelvis was of the same general appearance as that usually met with in cases of retained menstruation due to atresia of the vagina. It showed no tendency to adhere to the peritoneum or viscera, but could be sponged away perfectly clean. Careful search failed to show any traces of a small ruptured ectopic, nor did the character of the hemorrhage suggest this condition. The uterus was not distended, but this could easily be accounted for by the fact that the button had been removed for some time, and if it had been distended, it had had time to return to normal size. After removal of the exudate the patient made an uneventful convalescence; the pain was entirely relieved, and menstruation has since been normal.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,
PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

JOHN F. ANDERSON, M.D.,
FORMERLY DIRECTOR OF THE HYGIENIC LABORATORY, PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

An Outbreak of Anthrax Conveyed by Infected Shaving Brushes.—R. R. Elworthy, (*Lancet*, January 1, 1916) reports three cases of anthrax were definitely proved to be caused by infected shaving brushes. Of these, two, the D case and the B case, survived the disease while one, the W—P— case was fatal. Clinically, the W—P— case was an example of so-called erysipeloid anthrax, which is characterized by the insignificance or deferred appearance of pustules, rapidly spreading edema and a high mortality. It is usually seen in the neck or eyelids where the tissue is loose and cellular. Having proved the identity of the bacillus by culture and inoculation, an attempt was made to decide how the infection came about. The man's occupation in no way suggested anthrax. At the postmortem examination it was noted that the original area of infection came within the individual's shaving area. This suggested the idea that a new shaving brush might have been the cause of the infection after a small wound had been made by the razor edge. It was found that the man had been using a new razor for about a fortnight. This brush was obtained for examination and was found to be of poor quality, made of animal fiber, pig bristles horse-hair and cows' tails with a small amount of vegetable fiber. The brush was "lathered" with 20 to 30 c.c. of sterile broth made alkaline to phenolphthalein with 5 per cent. sodium hydrate. The washings were heated at 80° C. for fifteen minutes, centrifuged and the deposit collected in broth and distributed through three agar plates. Colonies which proved to be B. anthracis on subculture and inoculation grew. Some of the deposit was injected into a rabbit which died in three days from typical anthrax, and when this rabbit's blood was inoculated into a guinea-pig the latter died. In order to meet the objection that the infection of the brush was due to contact with an abraded anthrax lesion, unused brushes were examined, and out of the nine examined eight showed infection by B. anthracis on inoculation into guinea-pigs and six showed colonies of this organism on agar plates. A brush from the same manufacturer which had been used in the D case by a man who had contracted facial anthrax, was examined, but it was found that it had been thoroughly cleansed after use, which had probably removed the spores. However, when the ends of the hair, set inside the handle, were examined, they were proved to be infected by inoculating an animal with washings from them. The animal inoculated died in eight days from anthrax. Samples of the so-called "goat-hair" and hog-bristles which were used in the manufacture of these brushes were obtained. Nothing was found in the hog-bristles, but plates made from the washings of the goat-hairs were covered with colonies, half of which were anthrax. The animals inoculated with these washings died in thirty-nine hours from a mixed infection, cultures from the blood and spleen giving a few anthrax colonies. In an attempt to find the source of the hair infection, 30 pediculi found in a guinea-pig dead of anthrax were planted on the surface of an agar plate and 2 gave rise to colonies of anthrax. The last 2 brushes examined were associated with the B case, in which the patient was a youth, aged twenty-one years, who developed a malignant pustule on the back of the neck. A guinea-pig injected with the washings from the brush, died on the sixth day from anthrax. Since the lesion was on the back of the neck, it was thought that the infection was carried by the fingers or face-cloth. Another case of anthrax due to infection by a shaving brush is reported by E. H. Snell and E. W. G. Masterman in the *Lancet*, January 29, 1916. The clinical symptoms were characteristic of anthrax infection and smears of blood from around the pustule which developed showed anthrax bacilli as did smears from the spleen-pulp. No connection between the disease and his occupation or home-surroundings could be found. As the deceased had recently purchased a new shaving brush, it was thought that this might be the source of the infection. An examination was, therefore, made of the brush and anthrax spores found in it. Some of the brushes of the same make were purchased, and out of these, two were found to contain virulent anthrax spores.

The Physical Chemistry of Disinfection.—Norton and Hsu (*Jour. Infect. Dis.*, 1916, p. 180) in the first of a series of articles on the mechanism of disinfection studied from a physicochemical standpoint, record studies on the action of the hydrogen ion obtained from formic acid and the effect of neutral salts and of sodium formate on the rate of disinfection of B. typhosus by the hydrogen ion. This rate is shown to be proportional to the hydrogen ion, and is greatly increased by the presence of salts such as sodium chloride and sodium nitrate, but is decreased on the addition of sodium or ammonium formate to the acid. This latter action is due to the change in ionization produced, as shown by the fact that when isohydric mixtures of formate and acid are used, the rate of disinfection is increased in the same manner as with neutral salts. The conclusions from this study are that hydrogen ions are intimately concerned in acid disinfection, that salts act as catalyzers to increase the rate of action except where the salt and acid have a common anion, in which case there is a resultant effect due to the positive catalysis of the anion and the negative catalysis of the undissociated acid molecules.

Responsibility for Typhoid Fever.—In the case of Vennen vs. New Dells Lumber Company (*Public Health Reports,* vol. xxxi, No. 6, February 11, 1916) 154 N. W. Rep. 640 (October 26, 1915), the Supreme Court of Wisconsin decided that the death of an employee caused by typhoid fever which was contracted by drinking impure water furnished by the employer was the result of an "accident" under the terms of the Workmen's Compensation Law, and that the employer was liable.

Preventives of Typhoid Fever.—Methods for the Destruction of Body Lice.—GALEWSKY (*Deutsch. med. Wchnschr.*, May 27, 1915) gives an account of certain experiments for the destruction of lice found on the persons of Russian prisoners, and describes in some detail the measures adopted to stamp out typhus fever among such prisoners. In order that large bodies of troops might be quickly handled, large factories, such as sugar factories, were converted into stations for disinfecting soldiers and their clothing—some of these buildings being large enough to cope with from 12,000 to 15,000 prisoners and their clothing every day. The prisoners are first thoroughly washed with soap and water, while their clothing is being disinfected by steaming, with the exception of leather articles, which are subjected to dry heat. Galewsky made experiments to determine the most satisfactory method for the destruction of lice in buildings occupied by Russian prisoners nearly all of whom were infected by insects. All the cracks and corners were first washed with a 3 per cent. solution of cresol soap and were then plastered up. The clothing was hung loosely on lines in the building, with the exception of a bundle of shirts, which, for experimental purposes, was tied into a firm bundle. 25 kilos of sulphur were burned in the building, special sulphur stoves being used for the purpose. After three hours, the doors and windows were opened, and two hours later the building was occupied by the prisoners, who in the meantime had been bathed. It was found that the lice and eggs were completely destroyed except inside the parcel of shirts. Further experiments by Schlesinger showed that lice and their eggs were killed in two hours by sulphur dioxid vapors, but that it took two and a half hours or more for formaldehyde vapors to effect the same purpose. Dry heat was found to be effective in the destruction of lice and their eggs in one and a half hours, provided the articles to be disinfected were not closely packed. The general conclusion was that sulphur dioxid vapor is the cheapest and simplest, as well as the most reliable for the destruction of lice and their eggs in fomites and buildings.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
JOHN McCRAE, M.D., M.R.C.P.,
LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL
SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT,
BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL
VICTORIA HOSPITAL, MONTREAL,
AND
OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH,
PITTSBURGH, PA.

The Etiology and Experimental Production of Herpes Zoster.—In a series of recent publications Rosenow and his co-workers have attempted to establish a principle in bacterial infections, guiding the localization of microörganisms to particular organs or tissues. This process they speak of as the "elective localization" of bacteria. The intention of the authors is to prove the inherent quality possessed by bacteria for definite tissues. During all of the researches carried out by this group of workers no interest is displayed in the exact nature of the bacteria under discussion and there is an entire disregard of the part played by tissues in their antagonism or susceptibility to infection. For the bacteriologist it is difficult to follow the mental gymnastics of these workers, which permits them to draw sweeping conclusions from the assumptions which constitute the basis of the theory as well as from the garbled inconstant results of their animal experiments. The senior author appears to be familiar mainly with the tonsils and teeth as atria of infection of man's common ills. In these locations he claims to have shown the presence of infecting agents which, depending upon the object of the study immediately in hand, were the cause of appendicitis, cholecystitis, myositis, gastric ulcer, erythema nodosum, and, lastly, herpes zoster. In this study Rosenow and Oftedal (*Jour. Infect. Dis.*, 1916, xviii, 475) follow the same unscientific methods as have marked the previous investigations. The microörganisms obtained from the assumed atrium of infection are not determined as to their character by any of the known and accepted bacteriological methods. In some cases it is stated that a pure culture of a streptococcus was demonstrated. However, for the purpose of the experiments purity of cultures and analysis of microörganisms was deemed superfluous. To obtain from a tonsil (Case 267) "practically a pure culture" sufficed these authors to demonstrate the elective affinity of some undetermined type of streptococcus for the spinal ganglia. The material was obtained from the tonsils, gums or sputum of cases showing herpes zoster in various parts of the body. After brief growth of the collected material the culture, mixed or pure, was inoculated into animals. In this manner 10 cases, although the author in his summary speaks of 11 cases, in which some clinical data are given, are dealt with. In all at least 102 animals were treated but on 83 of these were used by the authors in making up their table of results. It would be interesting to know their findings in the other 19 animals. In 1 case it is claimed that a streptococcus was obtained from the spinal fluid of a case of severe unilateral thoracic herpes zoster. Such an important finding impressed them less than the results obtained in animals by the inoculation of mixed cultures from various sources. Hemorrhages were observed in the posterior ganglia and other tissues. Exactly what constitutes positive results in their animals is hard to say. Herpes is recorded as arising in the skin and eyelids. Apparently herpes in animals and that in man are two distinct conditions. "Rabbit No. 33, injected February 11, 1915, with the growth from 30 c.c. of ascites dextrose tissue broth. February 12, found dead. On removal of the skin several hemorrhagic vesicular hemorrhages were found over the left shoulder. A number of hemorrhagic vesicules were found at the juncture of the mucous membrane of the upper lip and the skin, etc." Lesions were also noted in this case in the tongue, appendix, sigmoid, stomach, liver, and spinal ganglia. Multiple foci of infection were observed in many cases, both in animals dying rapidly and those surviving a longer period. That numerous inflammatory areas were encountered in multiple tissue is, considering the dosage of living organisms, what would be expected in the use of various pathogenic bacteria. It is difficult to understand how these authors can claim elective localization by particular microörganisms in the experiments detailed.

Pathological Reconstruction of Organs (Metallaxis) and its Significance in Chronic Bright's Disease and Arteriosclerosis. — Jores (*Virchows Archiv*, 1916, 221, 14) expresses a general agreement with the classification by Volhard and Fahr particularly as regards the significance of primary renal arteriosclerosis in bringing about the small granular kidney which the Mannheim authors designate the mixed type. This form was claimed to result from the presence of arteriosclerosis and inflammation. Glomerular changes are commonly present either as a true inflammation or in epithelial desquamation within the glomerular capsule. It is difficult to say whether the examples studied by Jores and those by Volhard were the same. The former found evidence of degeneration about the glomerular capillaries. He believed that these changes were secondary to the arterial lesions similar to the atrophic changes which appear in the tubules which he speaks of as an atrophy of disuse. The atrophic changes of the epithelial structures vary, depending upon their position in the tubule. Indirectly the tubular changes result from the circulatory disturbances within the glomeruli. Not uncommonly the atrophy of one portion of the tubule is accompanied by an hypertrophy and hyperplasia in another. The proliferative changes in the tubules are a compensatory response to the degenerative process occurring diffusely in the kidney. The author states that the arteriosclerotic kidney is only distinguished from the mixed type by the degree in which the glomeruli are involved. He does not believe inflammation plays any particular role in either of the conditions. He applies a similar discussion to arteriosclerosis to justify the stand which he has taken in this subject. Inflammation, he believes, plays only a secondary role. He admits, however, that a variety of arterial lesions of the intima may be included under the term arteriosclerosis. He continues, however, to maintain that his hyperplastic and hypertrophic lesions are the important ones underlying arteriosclerosis. He places no weight upon the development of excess connective tissue in the absence of the described hyperplastic changes. He points out, however, that during the development of a particular pathological lesion in an organ there are commonly other tissue changes which are more or less of a compensatory character. This he names metallaxis. Admitting for arteries that one lesion may be followed by others in neighboring tissues the author is unwilling to supply the name arteriosclerosis to all proliferative and degenerative processes occupying the intima. He still demands a restriction of the term to the type described by himself. Thus, he states, the name arteriosclerosis is to be applied to the metallaxis of the vascular system in which lipoid degeneration and calcification are associated with hypertrophy and compensatory hyperplasia of the intima.

The Liver Changes in Wilson's Disease.—In 1912 Wilson described 12 cases of degeneration of the nucleus lentiformis associated with cirrhosis of the liver. During life the patients exhibited muscle weakness, dysphagia and involuntary, rhythmic, muscular twitching. Since the first description for this disease a number of new reports have been made by others. The majority of authors have commented upon the liver changes as differing from the usual atrophic portal cirrhosis. Some have suggested a congenital process of the liver with regeneration of the parenchyma. GEISSMAR (*Frank. Ztschr. f. Path.*, 1916, xviii, 305) reported a study of 4 cases with autopsy findings. The cases were all males, 3 of them brothers. Particular attention was given to the liver changes observed in 2 of the cases. Ascites was present in 2 cases and icterus in 1. In the liver there were no evidences of necroses though degenerative changes and pigment deposit were to be seen in the liver cells. Cirrhosis was marked. The fibrosis was irregular, often dividing the lobule into islands. Regenerative changes were also quite marked. The type of cirrhosis was not entirely comparable to either portal or syphilitic cirrhosis. The functional disturbances of the liver closely resembled portal cirrhosis. Splenic changes mainly resulted from portal stasis. No analysis was made of the cerebral lesions and no explanation is offered for the concurrent liver derangement.

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ORIGINAL ARTICLES

COMPARATIVE VALUE OF THE METHODS OF TREATING TETANUS.[1]

By Charles Langdon Gibson, M.D.,

SURGEON TO THE FIRST (CORNELL) DIVISION OF THE NEW YORK HOSPITAL, NEW YORK.

This study will not deal with (1) the prophylactic treatment of tetanus, (2) the surgical treatment of the wound or condition underlying the tetanus, (3) the general sedative treatment. The omission of these subjects is not due to any lack of recognition of their importance or necessity, but for the sake of brevity it is assumed that the last two requirements will be carried out so thoroughly as feasible.

My personal experience in the treatment of tetanus is limited to 8 cases; 3 cases died while 5 survived. Of these the first 2 fatal cases did not have the benefit of the more modern or radical methods, whereas the last 6 are characterized by having received antitoxin intraspinally. Of these 6 cases so treated since 1907 only 1 died, a mortality of 17 per cent. The following is a history of the cases, and I add one treated by my colleague, Dr. J. C. Roper, on the First Medical Division of the New York Hospital, which he has kindly allowed me to utilize:

Case I.—Sarah B. Previous operation by me for ovarian cyst. Convalescence normal. Operation at the General Memorial Hospital September 5, 1902, for similar condition. Convalescence

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[1] Read before the American Surgical Association, Washington, D. C., May 10, 1916.

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normal up to September 16; wound healed by primary union. That day pain in shoulder and back developed, with pain and stiffness in masseters. September 17, 20 c.c. of tetanus antitoxin was administered subcutaneously every six hours. There was general muscular twitching. From September 17 to day of death, September 23, patient kept quiet with morphin. Muscular rigidity general, most pronounced along spine. Masseters relaxed after 40 c.c. of tetanus antitoxin had been given. There is no definite record of the exact amount of antitoxin given or its equivalent in units. Incubation not known. If infection began at time of operation it would be eleven days; if it were due to liberation of tetanus organisms contained in the catgut allowance would have to be made for the disintegration of the catgut. Antemortem temperature, 109.8°. Tetanus developing after an abdominal operation rarely, if ever, recovers.

Case II.—John E. Policeman. Admitted to St. Luke's Hospital January 28, 1905. Died in twenty-four hours.

Present History. In attempting to stop a runaway horse he was thrown to the ground, cutting the little finger of his right hand. (Exact date of incubation unknown, but very acute.)

Chief Complaint. Irrational, convulsions.

Physical Examination. Head drawn back and neck and back rigid. Jaws fixed. Arms and legs are stiff. On dorsal aspect of terminal phalanx of right little finger there is a lateral wound.

Operation. Amputation of little finger. Exposure of brachial plexus and injection of 20 c.c. of tetanus antitoxin into nerves. Wound left open for future similar injections. Shortly after operation patient had slight convulsive contraction affecting entire body. At 1.45 A.M., January 29, severe convulsion. Patient very cyanotic. 9.45 A.M., dressing removed. 20 c.c. of tetanus antitoxin injected into the axillary nerves. 11 A.M., severe muscular contraction; patient died.

Case III.—Joseph G., aged forty years. Admitted to Hudson Street Hospital May 28, 1907. Discharged June 23, 1907. One week before admission, while at work, patient caught his right hand in a press, causing a severe compound fracture of the tip of the right thumb and the right index finger. The index finger was amputated at the metacarpal phalangeal joint, the operation being done in the dispensary. Patient returned daily for dressings, and was apparently improving, when on the day of admission he complained of stiff jaw, being unable to open his mouth more than a half inch. On May 29 the right brachial plexus was exposed under a general anesthetic and 60 c.c. of tetanus antitoxin injected into the nerve sheath. On May 31 two 20 c.c. doses of tetanus antitoxin were injected intravenously. Still marked rigidity of muscles of the cheeks, neck, and back. These were repeated on June 1. On June 2 still marked rigidity of back and thighs. Patient had involuntary spasms of the muscles of the thigh, causing him much pain. These spasms involved all muscles of the lower extremities. Patient was not incontinent at any time. Did not suffer with retention. Could move forearm freely, but movements of the right shoulder were less free, giving some discomfort. From June 3 to 11, 20 c.c. of antitoxin was injected intravenously daily (except June 6, 8 and 10). On June 12 there was marked improvement. Muscles of cheek, neck, and back less irritable and spastic. Thighs still rigid on slight palpation. On June 15 condition was much better. There was less rigidity in the thigh and the patient could open his mouth better and could flex the knees and thighs. Discharged cured June 23. Total amount of antitoxin 260 c.c., or 19,500 units (New York City Board of Health). Incubation unknown.

Case IV.—Edward Mc., aged thirty-four years. Admitted to Hudson Street Hospital June 10, 1908. Discharged July 2, 1908. Incubation not known. About one year ago an ulcer broke out on the right leg. It has been healed up twice but recurred. Slept last night in the park. Felt all right when he went to sleep, but when he awoke this morning his legs felt stiff and numb as "if asleep." Sat a while to rest them, and when he started away he fell, and because of stiffness of his legs and thighs was unable to rise. Found by ambulance surgeon doubled up on the curbstone. During the day he has had no pain, but every time he has endeavored to stand his legs would cramp and the muscles become tense and hard, also the pectoral muscles would cramp from time to time. He thinks that for the past two days he has had difficulty in swallowing. He had nothing to eat all day today, so did not notice anything the matter with his jaws. On June 11, 1500 units of tetanus antitoxin were injected intravenously. Two later doses of 1500 units each. He received daily thereafter until June 17, 1500 units of antitoxin (Board of Health) subcutaneously and 1500 units intravenously. June 18 and 19 the 3000 units were all given subcutaneously. On June 23 the patient was considered cured and he was discharged June 30 in excellent condition. Total amount of antitoxin 34,500 units; 15,000 units intravenously, 19,500 subcutaneously.

Case V.—John F., aged four years. Admitted to St. Luke's Hospital April 1, 1909. Died April 11, 1909. Run over by a street car and was dragged for some distance, the wheels passing over his left foot. Foot severely lacerated; all the phalanges were crushed and traumatically amputated. Both femora were fractured. On April 6, amputation at the lower third of the leg. April 8, 11.45 A.M., signs of tetanus first appeared. 7 P.M., 600 units of tetanus antitoxin were given intravenously. At 9.15 P.M., under chloroform anesthesia, the anterior crural nerve of the left thigh and its three branches were exposed. The nerve sheath was injected with 150 units of tetanus antitoxin. Sciatic nerve on left side exposed and sheath injected with 150 units. April 9, 1500 units of antitoxin were injected into the abdominal wall. Patient unable to open jaws at all. At midnight ♏vii tetanus antitoxin were given in the anterior crural and sciatic nerves. April 10, 1500 units were injected into the abdominal wall (9.30 A.M.); 12 M., ♏vii tetanus antitoxin were injected into the sheath of the anterior crural nerve on the left side and the sheath of the sciatic nerve; 8.30 P.M., 500 units of tetanus antitoxin injected intravenously; 10.45 P.M., 800 units of tetanus antitoxin were injected into the abdominal wall. Patient died April 11 at 7 A.M. Incubation seven days.

CASE VI.—Thomas B., aged thirty-two years. Admitted to the New York Hospital April 1, 1914. Discharged April 30, 1914. Incubation ten days. On day of admission the patient was caught between a train and the foundation wall at the Pennsylvania Station. Extensive laceration and traumatic amputation of all the toes of the right foot. Two days after admission the toes were amputated. Ten days after admission (eight days after operation) first signs of tetanus—stiffness of jaws. Antitoxin treatment begun at once. It consisted of the following:

	Intraneural units.	Intravenous units.	Intramuscular units.	Intraspinal units.	Subcutaneous units.
April 11	1,500	3,500			
	3,000				
April 12	5,000	3,000			
	3,000	10,000	7000		
April 13	....	9,000	....	8000	3000
April 15	....	7,500			
April 17	....	5,000			
	12,500	38,000	7000	8000	3000

Total, 68,500 units.

Also three doses, 1 c.c. (1 per cent.) of carbolic acid.

Last injection of antitoxin given the sixteenth day after admission. Discharged twenty-nine days after admission, cured.

This was a very severe case with opisthotonos, general convulsions, and coma. In the single intraspinal injection, done April 13, 4 ounces of clear fluid were drawn off under marked increased pressure, followed by the injection of 8000 units into the spinal canal. It was followed by a temperature of 105.2° and temporary aggravation of symptoms, but on April 16 his condition improved markedly. On April 20 all symptoms disappeared, his mouth could be opened normally, and he was discharged in excellent condition April 30.

CASE VII.—Glen T., aged ten years. Admitted to the New York Hospital October 9, 1914. Incubation seven days. Seven days ago he ran a nail into the sole of his foot. On the day of admission the first signs of tetanus appeared. The family physician administered one injection of tetanus antitoxin and sent the boy to the hospital. On admission the jaws were tightly locked; temperature 100°. Two hours later 3000 units of antitoxin (Board of Health) were administered intraspinally and 1500 about the wound. Next day the temperature was 106° and the patient had frequent general convulsions. Condition continued critical, and on October 13, under chloroform anesthesia, 5000 units were injected intraspinally. It was noted that the fluid was milky in appearance. Temperature 104° next day, but on October 15 all symptoms abated and he improved rapidly. On October 19 he could open his mouth nearly normally, and was discharged October 24 rapidly gaining in strength, with all tetanic symptoms and signs entirely gone.

Summary of Antitoxin Treatment.

	Intraspinal units.	Intravenous units.	Subcutaneous units.
October 9	3000	10,000	1500
October 10	....	9,000	
October 13	5000		
	8000	19,000	1500

Total, 28,500 units.

Case VIII.—Henry S., aged twenty-eight years. Admitted to the New York Hospital September 5, 1915. Incubation seven days. History of having fallen from a tree the day before, a distance of fifteen feet, landing with the right forearm outstretched. Examination shows compound fracture of forearm with low grade of infection. First signs of tetanus appeared September 11, six days after admission. Patient could not open his mouth. Under a general anesthetic 5000 units of tetanus antitoxin were injected intraspinally, 10,000 units intravenously, and 5000 units subcutaneously. Subsequent intraspinal injections done under local anesthesia. On September 27 condition began to improve. On October 11 he could open his jaws about one-half their normal capacity. On October 18 all evidence of tetanus had disappeared, and he was discharged October 31 with tetanus cured.

Summary of Antitoxin Treatment.

	Intraspinal units.	Intravenous units.	Subcutaneous units.	
Sept. 11	5,000	10,000	5,000	5000 in vicinity of ulnar nerve.
Sept. 12	4,000	10,000 12,000	5.000	
Sept. 13	5,000	10,000		
Sept. 14	5,000	15,000		
Sept. 15	5,000	17,000		
Sept. 16	5,000	10,000		
Sept. 18	....	10,000	15,000	
Sept. 19	....	.....	1,000	
Sept. 20	....	15,000		
	29,000	109,000	26,000	

Total, 169,000 units.

This was a very severe case, complicated by a very extensive and severe compound fracture.

Case IX.—Samuel N., aged twenty-four years. Admitted to the New York Hospital, service of Dr. J. C. Roper, September 5, 1915. Discharged September 25, 1915. Incubation three days (?). Patient was cut in palm of hand September 2 (three days before admission). Wound was dirty, but was well cleaned out and painted with iodin. That evening pain between the shoulders came on and the first signs of "lock-jaw." Since then these symptoms have grown steadily worse. On admission the neck is very stiff, both for lateral and anteroposterior movements. Cannot open the teeth more than 1.5 cm. Is unable to swallow. No history of convulsions. Superficial wound about 1.5 cm. long on the palm of the left hand. Not tender on pressure—not inflamed. On day of admission, under local anesthesia, lumbar puncture was done with injection of 3000 units of tetanus antitoxin intraspinally. This was repeated three times—(4500, 4500, and 5000 units). After the last injection, on September 8, he improved steadily. On September 12 the patient was up in a chair, and was discharged September 25, in good condition.

Summary of Antitoxin Treatment.

	Intraspinal units.	Intravenous units.
Sept. 5	1,500	10,500
Sept. 6	4,500	10,500
Sept. 7	4,500	10,000
Sept. 8	5,000	9,000
Sept. 9	....	15,000
Sept. 10	....	15,000
Sept. 11	....	15,000
	15,500	85,000

Total, 100,500 units.

Spinal fluid culture:
Sept. 5. Sterile five days.
Sept. 6. Sterile four days.
Sept. 7. Two spinal fluid cultures in agar tubes—both contaminated—Staphylococcus albus.

Although my personal experience is limited, I feel that the main reliance of the treatment of a well-marked case of tetanus should be along the lines employed in these last 4 cases, a combination of intraspinal and intravenous, also at the onset, local injection at the site of infection. With the more radical localization of the antitoxin in the nerve centers by the intraspinal method it seems to me unnecessary to make intraneural injections, and particularly if that procedure requires the administration of a general anesthetic and the time necessary for the careful dissection and exposure of the nerves. While the line of treatment outlined above impresses me most favorably, I realize that there are many divergent opinions, and that it is dangerous to draw conclusions from a limited number of cases even though successful. Statistics regarding the favorable results of any kind of treatment for tetanus are open to all the objections attending statistical information. Undoubtedly the cases of tetanus vary very greatly in their severity. Certain cases might really be classified as hyperacute, and it is doubtful if they will ever give favorable results. Others are distinctly of a very mild or chronic type; sometimes of a recurring type. Generally speaking the period of incubation has a general prognostic import; that is, short incubations seem to give rise to consistently severe symptoms, and *vice versa,* but even with this standard as a basis there are a good many sources of error. An important factor is the severity of the underlying wound or injury and the kind of treatment it receives or can receive. For that reason it is difficult or impossible to make any very satisfactory deductions from the experience obtained in the treatment of tetanus by wounds inflicted in war where the element of infection, surgical treatment, and after care play such a vital part. Therefore it seems that more logical deductions can be obtained from observation of cases of tetanus occurring in civil life. The nature of the remedial agents employed may also vary greatly, particularly as regards the strength of the antitoxin. In this country we shall soon have a pretty definite standard, thanks to the extraordinarily efficient and intelligent work of standardization of such agents by the United States Public Health Service and the increasing facilities for obtaining reliable preparations of antitoxin manufactured by State and municipal authorities in conformity with such standards. It has been shown by a number of observers that many preparations of tetanus antitoxin, especially those made abroad, vary tremendously in their strength and composition, and it would be manifestly impossible for a foreigner to utilize the recommendations contained in this paper without comparing the relative strength of the preparations at his disposal.

THE STANDARD OF MORTALITY. Broadly speaking, we ought to be able to establish two periods for our observations; one before the introduction of any so-called specific treatment, the treatment then being limited to the administration of a sedative whose necessity has always been recognized. We have two important statistics covering that era in the mortality of tetanus; during the Civil War 89.3 per cent. and the Franco-Prussian War 90 per cent. These observations, however, fall within the preantiseptic era. The paper of Ashhurst and John[2] (which contains the most satisfactory and intelligent exposition of the subject up to date) gives a series of 435 cases from 1897 to 1911, contributed by thirteen authors, with a mortality of 66 per cent. Another and most important factor is the promptness with which treatment is begun. It is my belief, though quite impossible to state it statistically, that this element is a most important factor, and I recommend breaking all speed laws to carry it out. We should be fully as prompt as in the treatment of an acute perforation of the gastro-intestinal tract. In a small proportion of cases it may be possible to recognize preliminary manifestations before the disease asserts itself in its classical manifestations. Localized cramps or twitching of the extremities may be recognized if anticipated. In 20 per cent. of cases it is stated that trismus is not the first symptom. The recognition of tetanus bacilli in the wound and the possible development of diagnostic serum reactions should be of assistance.

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[2] AM. JOUR. MED. SCI., June, 1913.

CHOICE OF TREATMENT. The number of remedial measures suggested is almost infinite. Three stand out today from all others, namely, antitoxin, magnesium sulphate, and carbolic acid. Only these three will receive here any serious consideration.

It may be interesting to study the various forms of treatment now being used in the European war, although a study of results will have to be deferred till accurate reports can be collected.

TREATMENT OF TETANUS IN THE PRESENT EUROPEAN WAR. One obtains the impression that at present (1916) the amount of tetanus is not very great, notwithstanding that the trench fighting and the severe cold with its consequent frost-bites would favor its development. There appears to have been a good deal of tetanus in the early conflict, but the increasing prophylactic treatment with antitoxin now seems to be keeping it in check.

One finds as much diversity in the treatment of tetanus in military life as in civil, and the customs seem to vary largely in the various countries.

TREATMENT OF TETANUS IN ENGLAND. The most satisfactory exposition of the treatment is contained in a little booklet *Memorandum on the Treatment of Injuries in War, Based on Experience of the Present Campaign*, July, 1915, published by the Royal Army Medical Corps. It is given in full, as it seems to be the best single comment on the methods available. It will be noted that the administration of tetanus antitoxin, and particularly the intraspinal method, is the method of choice:

"TETANUS. The heavily manured soil of the districts in which fighting has occurred frequently contains the spores of tetanus bacilli; these, in many wounds, are driven deep into the tissues and may find there the anaërobic conditions suitable for their development. Should the bacilli establish themselves in such a wound they give rise to toxins which have a great affinity for nervous tissues and produce the well-known symptoms of the disease.

"PREVENTION. A. *General Measures.* The steps advocated in other parts of this pamphlet for the cleaning, dressing and drainage of freshly received wounds, as well as for their appropriate surgical treatment, with a view to minimizing the risks of sepsis, are those which, if fully carried out, will also minimize the risk of tetanus. They need not, therefore, be further described here.

"B. *Special Measures.* These resolve themselves into the prophylactic use of tetanus antitoxin, a proceeding of well-established value.

"*Prophylactic Use of Tetanus Antitoxin.* Since in the first two months of the war more cases of tetanus occurred than had been anticipated, either by ourselves or our Allies, it was decided to direct that a preventive dose of serum should be given to every wounded man in place of leaving this, as had been done at first, to the discretion of the medical officer. The results have been excellent, and, in the last six months, there have only been 36 cases of the disease among those who received a preventive dose of serum within twenty-four hours of being wounded. That this is not due to the possible absence of the cause of infection from the soil is clear from the following facts: (1) Bacteriological examination of the wounds has often proved the presence of tetanus bacilli, although no tetanic symptoms have followed. (2) Many instances of slight trismus, or of localized tetanic spasms of a muscle or a group of muscles, have been reported, without the subsequent development of generalized tetanus. (3) Thirty-four cases of severe tetanus have been reported in this period among the very small fraction of wounded men who, for one reason or another, had not received a preventive dose of the serum within twenty-four hours. (4) A considerable number of wounded horses continue to develop the disease.

"The general use of preventive inoculation of the serum has also had an effect on the severity of the symptoms if, in spite of the preventive dose, the disease should subsequently develop. For example, of the 34 cases mentioned above, which did not have a preventive dose within twenty-four hours, 32 died, a case mortality of 94.1 per cent.; whereas of the 36 cases which occurred among the enormously larger class of wounded who *had* received a preventive dose, 28 died, a case mortality of 77.7 per cent.

"The preventive dose of 500 units should be given subcutaneously at a distance from the wound at the earliest possible moment, and the fact of inoculation, as well as the size of the dose, should invariably be recorded on the 'tally.' In severe wounds medical officers not infrequently give 1500 units; there is no objection to this, but at the same time there is no evidence that the smaller dose is insufficient if given promptly.

"It should be remembered that injuries other than those caused by bullets or shells may also become infected; several fatal cases have followed trivial injuries, for which the soldier did not report sick at the time, and others have followed on the gangrene due to frost-bite. It would be wise to give a preventive dose in all instances in which the danger of infection of a wound with contaminated soil may be presumed to exist.

"Several different preparations of tetanus antitoxin are in use. These have all been recently tested, and in each case they were found to contain at least the number of units claimed.

"(The question of Anaphylaxis is dealt with below.)

"*Influence of the Duration of the Incubation Period on the Severity of the Attack.* The general experience has been, as was to be expected, that the shorter the interval between the receipt of the wound and the appearance of the symptoms the smaller the chance of recovery. At the same time, cases have recovered in which the symptoms appeared six days after the wound, and cases have proved fatal where nineteen days had elapsed. The average incubation period of 43 fatal cases was 8.83 days, and that of 26 cases which recovered 11.57 days.

"TREATMENT WHEN THE DISEASE IS ESTABLISHED. A careful study has been made of 179 cases in which certain particulars which had been called for were furnished. Of these 179 cases, 140 have died, a case mortality of 78.2 per cent. Although this figure is disappointingly high, it must not be forgotten that the majority of these cases were also suffering from severe forms of sepsis, and in a considerable number of them the reporting officer stated that the tetanic symptoms had completely subsided under treatment, the patient dying from septicemia, gangrene, secondary hemorrhage, or other causes.

"A. *Local and Surgical Measures.* Steps should be taken to open up and clean the wound, if this has not already been done, and the freest possible drainage should be secured. The local application of strong antiseptics, swabbing with pure carbolic acid, the free use of hydrogen peroxide, and similar measures, have been tried, but appear to have had little influence on the course of the disease. Surgical interference of a grave nature, such as amputation of a limb, has been carried out in a number of instances; but such cases have almost always died, though not necessarily from the severity of the tetanic symptoms.

"B. *General Measures.* The patient should be kept in a perfectly quiet and darkened room, maintained, as far as possible, at an equable temperature. The avoidance of all external stimuli, likely to start a spasm, is to be aimed at, and some have advocated the bandaging of the eyes, the plugging of the ears with wool, the placing of the feet of the bed on rubber disks, etc., with this object in view. It is of great importance to maintain the strength of the patient by means of adequate fluid nourishment, given in small quantities at frequent intervals, and by the rectum if swallowing tends to induce spasm.

"C. *Use of Anesthetics and Sedatives.* As regards the former, chloroform is most commonly used, though ether has been preferred by some, especially when required for a small operation or for the dressing of a painful wound. Their value is well recognized. As sedatives, chloral hydrate, potassium bromide, and morphin are most frequently used for the purpose of controlling spasm, the first named being the most valuable. They are of undoubted value in this direction, but do not appear to modify the course of the disease to any great extent. Too frequent or too large doses may do harm. Chloretone, in doses of 30 to 40 grains in olive oil, given by the rectum, has been well spoken of for the same purpose of controlling spasm.

"D. *Carbolic Acid Method.* This has been given a trial in a considerable number of cases, usually in combination with tetanus antitoxin, but the results have been disappointing. The dosage must be considerable and the treatment must be kept up well into convalescence; in one case a relapse was reported to have followed its abrupt discontinuance. The following strengths of carbolic acid have been recommended:

I. 20 c.c. doses of a 1 per cent. solution.
II. 20 minim doses of a 2 per cent. solution.
III. 2 c.c. doses of a 5 per cent. solution.

"The inoculations are made either subcutaneously or intramuscularly every three or four hours, the interval between the doses being lengthened as the spasms diminish in frequency. In no case has any local trouble been reported, nor has carboluria followed even large and frequently repeated doses.

"E. *Magnesium Sulphate.* Three methods of employing this drug have been advocated: (*a*) The subcutaneous inoculation of doses of 2 c.c. of a 25 per cent. solution. (*b*) The subcutaneous inoculation of large quantities of a more diluted solution, Greely recommending the injection of a 1 to 2 per cent. solution in quantities varying from 1 pint to 1 quart every three hours, according to the severity of the case. (*c*) The intrathecal method. For this Philips advises the inoculation of a 25 per cent. solution, after withdrawing some of the cerebrospinal fluid, 1 c.c. being given for each 25 pounds of body weight, corresponding to 5 or 6 c.c. for a man of average size. The head of the bed should be propped up after the operation. The advocates of this method claim that it gives relief from pain, controls spasm, and ensures sleep. It has been used in this war chiefly by the intrathecal method, but, like carbolic acid, has not proved reliable.

"F. *Tetanus Antitoxin.* This is the only treatment as to the employment of which there has been anything like general agreement. It has been used in one form or another in almost every case, and when cure has resulted it has commonly been given the credit. Whatever method be employed it is clear that three general principles must be observed to obtain the best results: (1) It must be employed at the earliest moment possible; a dose of 1000 to 1500 units given at a time when there is little more than a fear that tetanus may develop, may influence the course of the disease favorably. (2) It must be given in large doses, and these should be frequently repeated until the symptoms show definite signs of amelioration. (3) It must be kept up, although in smaller and less frequent doses, well into convalescence, in order to obviate the tendency to relapse.

"The most favorable results appear to have been obtained by the employment, in the first instance, of the intrathecal combined with the intravenous methods, the subcutaneous method being used to reinforce the others in the succeeding days or to replace them as the symptoms diminish in intensity.

"*Dosage.* An initial intrathecal dose of 3000 units followed by the intravenous injection of doses ranging between 5000 and 20,000 units, according to the severity of the symptoms, has been reported in many instances to have had a favorable effect. In severe cases the intrathecal dose of 3000 units may be repeated the next day. The subsequent indications as to dosage depend upon the progress of the case; if this is favorable the above methods may be supplemented or replaced by the subcutaneous one, doses of from 5000 to 10,000 units being given every day or every second day.

"*Anaphylaxis.* Symptoms of this grave condition are well known in animals to follow the administration of a second dose of the same serum when the lapse of time between the two doses exceeds ten or twelve days. There was some reason to fear its occurrence in men who had received a preventive dose of tetanus serum after being wounded, and who, on account of the development of the disease after an interval of twelve days or more, were given therapeutic doses of the same serum. Again, a large number of men who have returned to the front after recovery from a wound are again wounded, and the question has been raised as to the possible danger of giving another preventive dose of serum after an interval of some weeks or months. It is, however, well known that man is much less sensitive to anaphylaxis than the guinea-pig and the rabbit, and this has been fully borne out by the experience of the war. In spite of close inquiries on the subject no certain instance of true anaphylaxis has been recorded. The few cases which have been mentioned in reports have, on investigation, turned out to be instances of serum sickness and to have had no grave results. It does not, therefore, appear to be justifiable to withhold the serum in the case of a man wounded for the second time; at all events, it appears better to run the small and chiefly theoretical danger of anaphylaxis than the very grave one of tetanus.

"In cases in which there is reason to fear the occurrence of anaphylactic shock, various procedures have been recommended to lessen the danger. The majority of these are "fractional" methods of administering the serum, a preliminary inoculation of 2 or 3 drops of the serum being given, in dilution, followed in five minutes by a dose of 0.5 c.c. If no untoward symptoms result it is said that the full dose may safely be inoculated ten minutes later. A similar fractional method has been advised if the intrathecal methods are selected, but there has been no opportunity of judging of their value. Administration of the serum under chloroform anesthesia is also said to lessen the danger. If symptoms of shock should develop in spite of these precautions, adrenalin has been stated to be useful, given intravenously in high dilution if the symptoms are urgent, hypodermically in less urgent condition in doses of a few minims of a 1 to 1000 solution."

Treatment of Tetanus in Italy. Dr. Carlo Savini, of New York City, who has recently returned from the Italian war zone, writes under date of October 22, 1915, as follows:

"The consensus of opinion in Italy seems to be very favorable to the Bacelli treatment of tetanus. It is claimed to give only 17 per cent. mortality, while the symptomatic (or expectant) and the antitetanic serum treatment give from 50 per cent. to 78 per cent. mortality.

In the war zone the prophylactic injection of antitetanic serum is compulsory for all the wounded, and I was told that very few cases of tetanus are found.

The treatment of tetanus is left to the judgment of each doctor, and it is not possible now to state how often the Bacelli treatment is being used and what the results are.

In conclusion, in Italy everybody agrees in the prophylactic value of the serum. In the therapy of tetanus the treatment of Bacelli seems to be the most favored; next is the treatment with injection of magnesium sulphate solution, and last the treatment with antitetanic serum."

Professor R. Bastianelli writes under date of December 12, 1915:

"I am not able to answer satisfactorily your question about the treatment of tetanus in Italy. The present war has given ample occasion to collect experience on that argument, but the results are not yet tabulated. Prior to the war, Bacelli's method was used extensively by us and the reports have been satisfactory. It is possible, however, that many unfavorable cases have not been reported. The antitoxic method, either with Tizzoni's antitoxin or with Behring's serum, has been employed extensively, and so far as I know with rather good results in cases with late onset and slow course, while in the so-called acute cases the results have been very poor and in my experience constantly bad. I have used the serum intravenously and intraspinally at the same time, giving also large doses of chloral and intramuscular injections of magnesium sulphate."

Treatment of Tetanus in France. In France there is also no distinct line of treatment. October 11, 1915, Dr. Charles Walther writes me:

"I find it difficult to give you exact information, as I doubt if there is a single method of treatment of tetanus which is generally accepted. In addition to the classical treatment by heat, dark room, administration of chloral, I find there is a tendency to employ more and more antitetanic serum in large doses, 40 to 50 to 60 cm. daily subcutaneously or intravenously. Intraspinal injections in considerable amounts, between 40 and 60 c.c., every second day, with head and trunk lowered, seem to have given good results. Personally, I have had a certain number of successes in the intravenous and subcutaneous injections of antitoxin in large amounts, particularly of peripharyngeal injections in the subhyoid region at the base of the tongue.

"I believe I was the first, fourteen years ago, to make intraspinal injection of antitetanus serum in a case at the La Pitié Hospital. I have personally no experience in the use of magnesium sulphate or carbolic acid."

TREATMENT OF TETANUS IN BELGIUM. The treatment most favored by Dr. Depage when I saw him in February, 1915, was the antitetanus toxin, but I do not think he ever used it intraspinally.

I have not heard directly from the other fronts and can only surmise as to the methods employed. Stolbnyak states, in the *Russkiy Vrach*, Petrograd, summarized in the *Journal of the American Medical Association*, January 15, 1916, page 232:

"The best symptomatic results were obtained with chloral hydrate, from 1 to 7 gms. daily given by the mouth or rectum. For spasmodic contracture of the intestines and bladder hypodermic injection of from 0.5 to 1 gm. of a pituitary extract gave good results. Warm baths at 100° F. also proved effectual in symptomatic treatment. No benefit could be detected from treatment with antitetanus serum, intravenous or intraspinal; from 3 per cent. phenol solution; suspensions of pigs' brains; calcium lactate three times daily in doses of 30 drops of a 10 per cent. solution, or from magnesium sulphate in hypodermic injections of from 2 to 14 c.c. of a 25 per cent. solution, or by intraspinal injection of 15 c.c. of a 10 per cent. solution."

In Germany the treatment seems to be most varied, and includes a number of methods which would seem to have little but their novelty to recommend them. Violet light, salvarsan, ascitic fluid from cured patients, emulsion of pigs' brains, intravenous injections of ether, etc.

The method which seems to be most in favor is the magnesium sulphate treatment, particularly when injected into the spinal canal. Kocher's favorable report on its use seems to be responsible for its popularity.

COMPARATIVE CLAIMS OF ANTITOXIN TREATMENT, MAGNESIUM SULPHATE AND CARBOLIC ACID. As has been stated before, it seems quite impossible at present to establish anything like a statistical investigation with any hope of accurate results. Only if very large groups treated under similar conditions should show marked discrepancy in results would it be safe to draw any deductions.

The Antitoxin Treatment. The antitoxin treatment may be divided into (*a*) subcutaneous administration, (*b*) intravenous, (*c*) intraspinal, (*d*) intraneural, (*e*) intracerebral. The last method we can dismiss, as it is no longer employed, and gave very bad results; the other methods promise better.

(*a*) The subcutaneous method, it is believed, lacks efficiency and should be used only as an adjuvant to the other methods.

(*b*) The intravenous administration is a distinct advance as regards efficiency and rapidity of results. My belief is, however, that it should be considered as an accessory rather than the main line of treatment.

(*c*) The intraspinal method appeals to me as complying most with the indications, namely, locating the antitoxin most directly to the lesion itself. Ashhurst and John have presented conclusively the evidence that the toxin of tetanus reaches the spinal cord by the peripheral nerves. They state that "the nearer the toxin gets to the spinal cord the more impregnably intrenched does it become in the nerve tissue."

It is not easy to determine who was the first responsible for the idea of injecting the antitoxin intraspinally. I find no mention of it prior to Schultze's article in the *Grenzgebiete der Medizin und Chirurgie.*

Personally, I have been much impressed with the evidence furnished by the experimental work and clinical results of Dr. W. H. Park and Dr. M. Nicoll, Jr., from the laboratory of the New York City Board of Health. I may state that in all my successful cases here reported the treatment has been conducted entirely on the lines laid down by these gentlemen and with their advice and coöperation. In the *Journal of the American Medical Association*, June 12, 1915, Nicoll reports 20 cases treated with the chief reliance on intraspinal injections, with 4 deaths. These cases represent an average severity, were under the care of different physicians and under varying conditions.

They recommend (1) from 3000 to 5000 units in the lumbar region of the spinal canal, preferably under an anesthetic,[3] the volume of fluid injected being brought up to 10 or 15 c.c. by the addition of sterile or normal saline, the exact amount being regulated to the age of the patient and the amount of spinal fluid withdrawn; (2) 10,000 intravenously at the same time; (3) repetition of the intraspinal dose in twenty-four hours; (4) subcutaneous dose of 10,000 units three or four days later.

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[3] This recommendation of the author, I think, will be only exceptionally necessary, *e. g.*, in the case of children. It is important to remember this fact as the recommendation to *give* an anesthetic might deter some from utilizing this valuable method.—C. L. G.

The above directions may suffice in a case of ordinary severity, but we believe that many cases will have to receive more antitoxin intraspinally than the two injections recommended and a good deal more intravenously. Case VIII received 6 injections, 29,000 units of antitoxin intraspinally and antitoxin in other forms up to 169,000 units.

I am inclined to think that in the future we shall use greater amounts of antitoxin intraspinally and especially in the initial dose. Dr. Boyd, of Springfield, recently reported a case of a young child in which treatment was begun at the end of a week, the child being then apparently moribund. Under an initial dose of 15,000 units intraspinally the patient made a prompt response and good recovery. I am inclined to think that in future cases of great severity I shall also begin with as large or possibly even larger dose.

In a mild case some question may arise as to whether more than the initial intraspinal dose should be administered. If improvement becomes manifest at once the second intraspinal dose may be well withheld, but the antitoxin intravenously should be administered daily until the improvement is certain. A guide to the necessity for antitoxin treatment may be had in estimating the antitoxic contents of the blood. This procedure, however, requires the coöperation of an expert worker, and is time-consuming and not really necessary. There is probably very little danger in overdoing the dosage so long as active symptoms of tetanus are present. The fluid withdrawn from the spinal canal after the preliminary injection of antitoxin has a milky tinge, but was found in our cases to be quite sterile.

(*d*) If we accept the value of the intraspinal injection of antitoxin there seems to be little call for intraneural injections which some fifteen years ago were extensively employed and apparently with an improvement over the then commonly used methods. Unless better evidence can be furnished of the value of intraneural injections they can be eliminated, for they require the performance of a formal operation under an anesthetic which in the patient's grave condition is inadvisable, besides being a more formidable procedure than the simple injection intraspinally. If we accept the doctrine that the intraneural injection is superfluous we can also apply this dictum to the amputation of an extremity.

MAGNESIUM SULPHATE. This treatment was originated in the United States by Meltzer and Auer. In the *Journal of the American Medical Association*, March 25, 1916, Meltzer writes of the "Inhibitory Properties of Magnesium Sulphate and their Therapeutic Application in Tetanus." He says:

"The action may appear to some as merely a symptomatic one; it relieves the convulsion. But even if this would be indeed its only favorable effect, it would be of inestimable value, since the suffering in tetanus and the fatal outcome of this horrible disease is nearly exclusively due to the consequences of the tetanic symptoms. And I may assert that no other remedy is capable of relieving the furious symptoms to such a satisfactory degree as do the injections of magnesium sulphate."

Magnesium sulphate can be administered intraspinally, subcutaneously, intravenously, intramuscularly plus ether inhalation. Meltzer summarizes the treatment as follows:

"The best general plan for treatment of tetanus would seem to be as follows:

"In each and every case of tetanus, 1.2 c.c. of a 25 per cent. solution of magnesium sulphate should be given by subcutaneous injection three or four times a day throughout the entire disease.

"When the disease is complicated by severe tetanic attacks, 1 c.c. of a 25 per cent. solution for every 10 kg. (20 pounds) body weight (in adults) should be given by the intraspinal method.

"When the disease is attended by immediately dangerous tetanic complications, from 2 to 3 c.c. per minute of a 6 per cent. solution of magnesium salts should be given then by an intravenous injection until dangerous symptoms subside or the respiration becomes shallow or too slow.

"When the respiration seems to become impaired in consequence of the administration of magnesium salt by the intravenous, intramuscular, or subcutaneous methods, calcium chloride should be injected in the manner described above.

"It is advisable to have at hand an apparatus of intrapharyngeal insufflation ready for use whenever the respiration becomes slow or shallow.

"Finally the simultaneous treatment by antitetanic serum should not be neglected."

No statistics are given in support of the success of this method of treatment. Reference is made to a favorable report by Kocher.

This treatment was employed at the time of its development in New York City; but the general impression is that it has too many dangers and drawbacks *per se*, particularly in paralyzing the respiration. Its intraspinal administration undoubtedly checks the convulsions more speedily than any other method. I should prefer however, to substitute for it the inhalation of a general anesthetic to a very slight degree as used to be done fifty years ago.

The method was employed quite a little following Meltzer and Auer's original description. Of late there seems to have been little attempt to use it in America, but in the present war it seems to stand out as prominently as any one method in Germany and to some extent in other countries.

Cloetta[4] warns against the use of magnesium sulphate and notes its resemblance to the action of curare which was used in tetanus fifty years ago.

Carbolic Acid Treatment. This treatment was initiated by Bacelli, according to Ashhurst and John, in 1888. The mortality claimed for it is the lowest of all, 17 per cent. It seems remarkable that it has not come into more general use especially in America. It is administered, according to Ashhurst and John, 1 c.c., 1 per cent. solution, every few hours, perferably into the muscles along the spine, until 80 or 100 centigrams are given in twenty-four hours.

Sainton[5] reports 22 cases of tetanus treated in the French Army Hospitals by the Bacelli method, with 16 deaths. This is not a very favorable showing for the method, but it must be remembered the difficulties of estimating the results of subjects wounded and treated under war conditions.

Summary of Proposed Choice of Treatment. As I have stated before, it is presumed that the wound treatment will be that suitable to the injury and particularly to the most efficient form of drainage and liberation of sloughs, removal of foreign bodies, etc., that may harbor tetanus germs or favor their development. I doubt if today we are justified in performing an amputation for the relief of tetanic manifestations as in the intraspinal administration we have gone a step further in efficiency. Likewise, I will omit the questions of nursing and the use of sedatives. One sedative, however, should be alluded to as it has been thought to have curative qualities *per se*, namely the chloretone treatment advocated by Hutchings.[6]

I should also be inclined to make a trial of atropin as a method of controlling spasm, as this drug has lately impressed me greatly in the treatment of spasmodic contraction of the pylorus.

Antitoxin treatment should be begun immediately on suspicion of tetanus developing rather than waiting for the classical symptoms. If this principle is firmly established, I believe we shall have done much to lessen the dangers of the disease. Antitoxin should be given at once, first into the wound or region of the wound, say 1500 units, intraspinally, without an anesthetic, unless the treatment of the wound calls for the administration of a general anesthetic, 5000 to 20,000 units. In the course of the first twenty-four hours, in addition to the above, 10,000 to 20,000 units should be administered intravenously in divided doses, say two or three. Antitoxin intravenously from 5000 to 15,000 units should be given next day no matter whether the symptoms remit or increase. On the third day if, notwithstanding the treatment, the patient's symptoms continue very severe or appear worse the intraspinal

[4] Correnspondenz-Blatt f. schweizer Aerzte, 1915, No. 3.

[5] Journal de Chirurgie, September, 1915.

[6] Annals of Surgery, vol. l.

treatment should be repeated. The intraspinal, of course, gives temporary increase of symptoms and steep elevation of temperature but this fact need not of itself cause alarm. If after this treatment the patient holds his own or improves the intraspinal need not be repeated but the daily injection of antitoxin intravenously should be given until obvious remission or cure results.

The severity of the cases will, of course, vary and the resulting treatment will depend on this factor. Attention is called to Case VIII, who received a total of 169,000 units, which included 29,000 units given intraspinally in six sessions, in this case, daily, although I doubt if this frequency is often indicated.

The series of cases I have reported is, of course, small, and I am fully aware of the dangers of deducing results from such small material. On the other hand, I have the impression, though I find it hard to put into words, that, although many of these cases were of the severest type and very ill, we had, particularly in the intraspinal method, complete control of the situation. With this feeling of confidence, therefore, I should hesitate to offer any other method of treatment until there is better evidence of the superiority of these other methods.

THE PATHOLOGIC CHANGES IN THE SYMPATHETIC SYSTEM IN GOITER.*

By Louis B. Wilson, M.D.,
ROCHESTER, MINNESOTA.

The amount and character of the pathologic changes in the sympathetic ganglia removed at operation or at autopsy from patients with exophthalmic goiter have been studied by other observers, meagerly and rarely by modern methods. I have reviewed elsewhere[1] the literature of previous reports. So far as the findings have been positive, they have shown that in exophthalmic goiter the cells of the sympathetic ganglia exhibit various stages of degeneration. The paucity and incompleteness of the reported observations, however, together with Cannon's[2] recent experimental production of some of the symptoms of exophthalmic goiter in cats by constant stimulation of the thyroid through the sympathetic system, have warranted a more careful study of the material accumulating in the Mayo Clinic.

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* Read before the Association of American Physicians, Washington, D. C., May 10, 1916.

Previous Report in the Present Series of Observations.

Durante and I[1] have recently reported our observations on twenty superior cervical sympathetic ganglia removed at operation from sixteen patients with hyperplastic toxic (exophthalmic) goiter. Our findings may be briefly summarized as follows:

1. Definite histologic changes in the cells of the cervical sympathetic ganglia in hyperplastic toxic (exophthalmic) goiter occurred in all cases examined.
2. These histologic changes consisted of various stages of degeneration, namely (*a*) hyperchromatization, (*b*) hyperpigmentation, (*c*) chromatolysis, and (*d*) atrophy or (*e*) granular degeneration of the nerve cells.
3. Some of the ganglia contained cells resembling the partially differentiated cells found in the ganglia of infants.
4. Accompanying the more advanced changes in the ganglion cells were similar degenerative changes in the nerve fibers and an increase of connective tissue throughout the ganglion, but especially in the outer and middle coats of the vessels and in the periganglionic tissue.
5. So far as could be determined from the small number of observations, the pathologic changes in the cervical sympathetic ganglia were parallel to the stage and intensity of the symptoms of hyperthyroidism and to the hyperplastic and regressive changes in the thyroid.

Material for the Present Study.

The present report is based on a study of the cervical and other sympathetic ganglia removed at autopsy from twelve patients dying during the course of exophthalmic goiter. The observations have been controlled by similar studies on sympathetic ganglia removed at autopsy from nine patients dying of diseases other than exophthalmic goiter, and by studies on gasserian ganglia removed at operation from six patients with trifacial neuralgia.

All ganglia removed at operation were fixed within five minutes after removal, and the material from autopsies was fixed within three hours after death. Some portions of ganglia were examined in frozen sections of the fresh tissue. The remainder of the specimen or specimens was fixed in 10 per cent. formalin. Selected blocks were cut frozen without embedding and the sections stained with Sudan III or by Nissl's method. Other blocks were embedded in paraffin and cut in serial sections, which were stained with hematoxylin-eosin, by Weigert-van Geison's method for connective tissue, by Weigert-Luden's method for myelin,[3] and by Held-Nissl's method for distribution of chromatin. Other blocks were used for silver impregnation by Ramon y Câjal's,[4] Levaditi's,[5] or Bielschowsky's methods. Others were fixed and stained by

Bensley's[6] acetic-osmic-bichromate method for mitochondria. The most satisfactory results were obtained by the use of Sudan III, Held-Nissl's, Ramon y Cajal's, and Bensley's stains.

PROTOCOLS.

CASE 1 (A156,845).—The patient was a female, nineteen years of age, who had had severe symptoms of hyperplastic toxic goiter for five months. Recently the thyroid had enlarged very rapidly. The patient died of hyperthyroidism a few days after coming to the Clinic, without having been operated on. At autopsy, three hours and forty minutes after death, there was found marked hyperplasia of the thyroid, marked exophthalmos, symmetrical brown pigmentation of the conjunctivæ, marked emaciation, petechial hemorrhages in the skin, in the parietal peritoneum of the true pelvis, and elsewhere in the pelvic organs, marked hypertrophy of the myocardium of the left ventricle, slight nodular sclerosis of the coronary arteries, and fatty changes in the intima. The thymus weighed 80 grams.

Microscopically, the thyroid showed progressive advanced hypertrophy and hyperplasia, Type B[7]. The superior cervical ganglia showed very marked hyperpigmentation and extensive granular degeneration of the cells, many of which were atrophic or consisted of only small masses of pigment.

CASE 2 (A153,535).—The patient was a female, nineteen years of age; for five months had shown symptoms of severe exophthalmic goiter. The systolic blood-pressure was 180, diastolic 75, pulse-rate 150 to 168. After two weeks' preparation the left superior thyroid vessels were ligated. The temperature remained normal and the pulse fluctuated from 100 to 118. Death occurred three days after operation. The macroscopic findings at autopsy, made three hours and fifteen minutes after death, were those of severe exophthalmic goiter.

Microscopically, the thyroid showed progressive advanced hypertrophy and hyperplasia, Type B[7]. Many of the cells from the cervical sympathetic ganglia were in the state of advanced degeneration noted in Case 1, though not nearly so many cells were affected (Fig. 1).

CASE 3 (A144,809).—A female, thirty years of age; had had severe symptoms of exophthalmic goiter for eight months. At the time of examination the systolic blood-pressure was 165, diastolic 70, and pulse-rate 128. The left superior thyroid vessels were ligated, and four months later the right superior thyroid vessels were also ligated. Two weeks after the second ligation the right lobe, isthmus, and pyramidal lobe of the thyroid were extirpated. Death occurred the following day. At autopsy, two hours and thirty minutes after death, an advanced chronic myocarditis with fatty degeneration and advanced degenerative changes in the liver and kidneys were found.

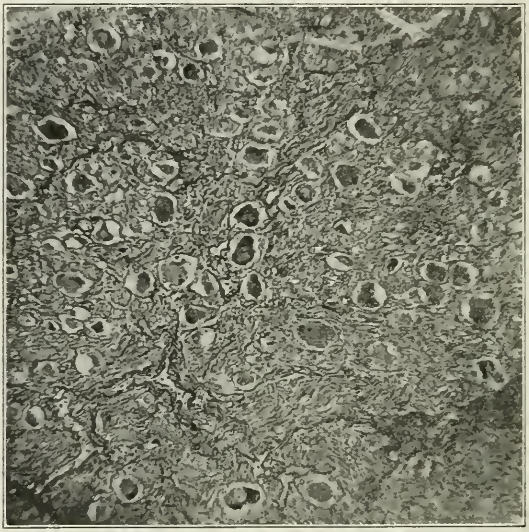

Fig. 1 (Case 2).—Section of left superior cervical sympathetic ganglion, silver impregnation, 5 microns, × 120 diameters. Advanced degeneration of many cells.

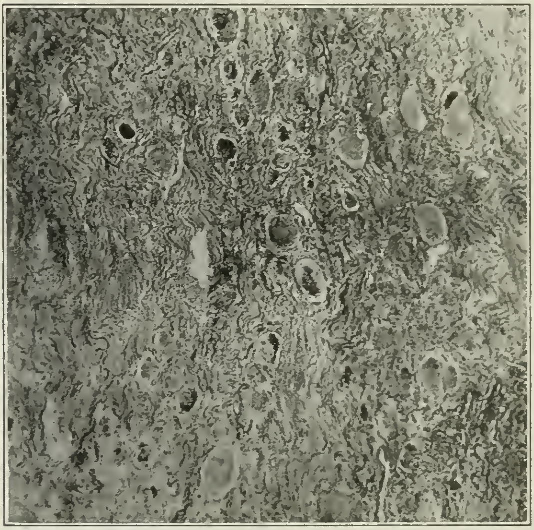

Fig. 2 (Case 3).—Section of left superior cervical sympathetic ganglion, silver impregnation, 5 microns, × 120 diameters. A few normal cells, many showing advanced degeneration.

Microscopically, the thyroid showed early regressive advanced hypertrophy and hyperplasia, Type C–1[7]. In the cervical sympathetic ganglia a few cells were apparently normal. Many showed varying degrees of hyperpigmentation and granular degeneration (Fig. 2).

Case 4 (A136,418).—The patient, a female, twenty-five years of age, had shown symptoms of exophthalmic goiter for two years, with marked increase in severity during the last three weeks. At the time of examination the systolic blood-pressure was 145, and diastolic 80. The left superior thyroid vessels were ligated, and five days later the right superior vessels were ligated also. Four and a half months later the right lobe, isthmus, and a small portion of the left lobe of the thyroid were resected. The patient died nine days after the operation. At autopsy, eight hours after death, the macroscopic findings were a hypertrophied thymus, acute myocardial degeneration, and dilatation of the heart, congestion and degeneration of all parenchymatous organs, and severe purulent bronchitis. The cervical sympathetic ganglia were noticeably enlarged.

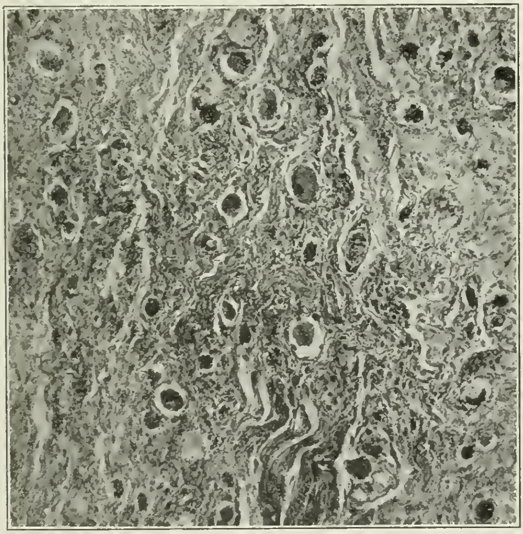

Fig 3 (Case 4).—Section of right superior cervical sympathetic ganglion, silver impregnation, 10 microns, × 120 diamters. A few normal cells, many in varying stages of degeneration.

Microscopically, the thyroid showed early regressive advanced parenchymatous hypertrophy and hyperplasia, Type C–1[7]. The ganglia showed a few fairly normal cells, but many others in varying stages of degeneration (Fig. 3).

Case 5 (A11,264).—This patient was a female, thirty-three years of age, who had had symptoms of exophthalmic goiter beginning two years and five months previously. At the time of examination the systolic blood-pressure was 138, diastolic 90, and pulse-rate 138. The left superior thyroid vessels were ligated, and two weeks later the right superior thyroid vessels were ligated. Two and three months after the last ligation, hot-water injections were made into each lobe of the thyroid, and three weeks after this, or four and a half months after the first ligation, the right lobe and isthmus of the thyroid were extirpated. The patient's pulse-rate increased to 140, and she died twenty-four hours after the operation. At autopsy, two hours and thirty minutes after death, the principal macroscopic findings were acute and chronic myocardial degeneration, with a dilated heart, general parenchymatous degeneration not so severe as usual in exophthalmic goiter, and chronic nephritis.

Microscopically, the thyroid showed early regressive advanced hypertrophy and hyperplasia, Type C–1[7]. A few cells in the cervical sympathetic ganglia were normal. Many showed varying degrees of hyperpigmentation and granular degeneration.

Case 6 (A149,095).—The patient, a female, twenty-eight years of age, had shown symptoms of exophthalmic goiter for six years, with a maximum severity within the first year. At the time of examination she had slight exophthalmos, a systolic blood-pressure of 150, a diastolic of 80, and a pulse-rate of 120. The left superior thyroid vessels were ligated, and two weeks later hot-water injections were made into the right lobe of the thyroid. One week after this the right superior thyroid vessels were divided and the ends ligated separately. Two weeks after the last operation the patient died. At autopsy, one hour after death, the principal macroscopic findings were bilateral lobar pneumonia with infarction of right upper lobe and hypertrophy and dilatation of the heart.

Microscopically, the thyroid showed a regressing advanced hypertrophy and hyperplasia, Type C–2[7]. The cervical sympathetic ganglia showed many cells apparently normal, a few in advanced stages of degeneration, and a very few in intermediate stages of degeneration.

Case 7 (A-135,172).—The patient, a female, twenty-nine years of age, had had goiter for sixteen years, with moderate symptoms of thyrotoxicosis for twelve years, the maximum severity of toxic symptoms having been attained about four years ago, since which time there had been some abatement. At the time of examination the systolic blood-pressure was 175, the diastolic 78, and the pulse-rate 114. The left and right superior thyroid vessels were ligated, and four months later the right lobe, isthmus, and a small piece of the left lobe of the thyroid were extirpated. The patient died one week after operation. At autopsy, two hours after death, the macroscopic findings were an hypertrophied thymus, bilateral emphysema, acute splenitis, and chronic nephritis, with congestion.

Microscopically, the thyroid showed advanced regressive changes on chronic hypertrophy and hyperplasia, Type C–2[7]. The superior cervical sympathetic ganglia showed many cells apparently normal and a few in advanced stages of degeneration. The total number of cells was apparently much reduced (Fig. 4).

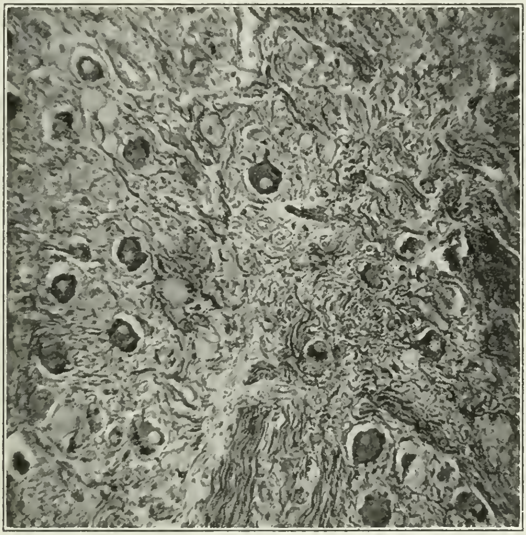

Fig. 4 (Case 7).—Section of right superior cervical sympathetic ganglion, silver impregnation, 5 microns, × 120 diameters. Marked reduction in the number of cells, many apparently normal, and a few in advanced stages of degeneration.

Case 8 (A109,170).—This patient, a female, forty-seven years of age, had noticed enlargement of the thyroid for four years, but symptoms ascribable to thyrotoxicosis began only one year prior to the enlargement. At the time of examination the systolic blood-pressure was 140, diastolic 45, and pulse-rate 120. The right and left superior thyroid vessels were ligated. The patient improved steadily in health for eight or nine months, and then began to lose appetite, weight, and strength. A year after the first operation, several hot-water injections into the thyroid were made. The general health improved, but there was a rise in blood-pressure to 166 systolic, 90 diastolic, and a rise in pulse-rate to 140, six months after the injections. One month later the pulse-rate was 176. Death occurred a month after this, or one year and eight months after the first operation,. At autopsy, three hours after death, the macroscopic findings were hypertrophy and dilatation of the heart, chronic cholecystitis, and parenchymatous degeneration of all organs.

Microscopically, the thyroid showed advanced regression on an old parenchymatous hypertrophy and hyperplasia, Type C–3[7]. The superior cervical sympathetic ganglia showed a great reduction in the total number of cells, many of the remaining ones of which, however, were normal, while a few were in advanced stages of granular degeneration.

Case 9 (A-147,479).—The patient, a female, forty-four years of age, had had thyroid enlargement for thirty-two years, with symptoms of thyrotoxicosis beginning five years ago and gradually increasing to the present time. At the time of examination the patient had lost weight from 150 to 114 pounds. The systolic blood-pressure was 122, diastolic 80, and the pulse-rate was 120. Patient died without operation. At autopsy, two hours and forty-five minutes after death, the macroscopic findings were a medium-sized retrotracheal thyroid, hemopericardium, and right hemothorax with adhesions, and acute parenchymatous degeneration with fatty changes in the heart, liver, and kidneys, and chronic nephritis.

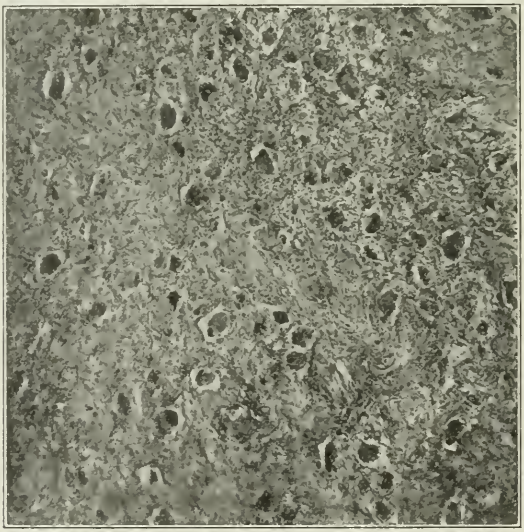

Fig. 5 (Case 9).—Section of right superior cervical sympathetic ganglion, silver impregnation, 10 microns, × 120 diameters. Many normal cells, many hyperpigmented, and a few in advanced stages of degeneration.

Microscopically, the thyroid showed advanced regression on chronic parenchymatous hypertrophy and hyperplasia, Type C–3[7]. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Of those present, many were normal, and a few were in advanced stages of degeneration (Fig. 5).

Case 10 (A67,759).—The patient, a female, fifty years of age, had had enlargement of the thyroid for twenty years, with mild symptoms of thyrotoxicosis beginning coincident with the thyroid enlargement and lasting for three years. Six months previous to examination, the symptoms of thyrotoxicosis returned. At the time of examination, the patient was emaciated, the pulse-rate was 200, with a cardiac arrhythmia growing progressively worse. Death occurred three days after examination. At autopsy, one hour after death, the principal macroscopic findings were enlarged thyroid, myocarditis, atrophic and fatty changes in the liver, and chronic nephritis.

Microscopically, the thyroid showed advanced regressive changes in parenchymatous hypertrophy and hyperplasia with some adenomatosis, Type C–3[7]. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Most of those present, however, were fairly normal while a few showed advanced degenerative changes.

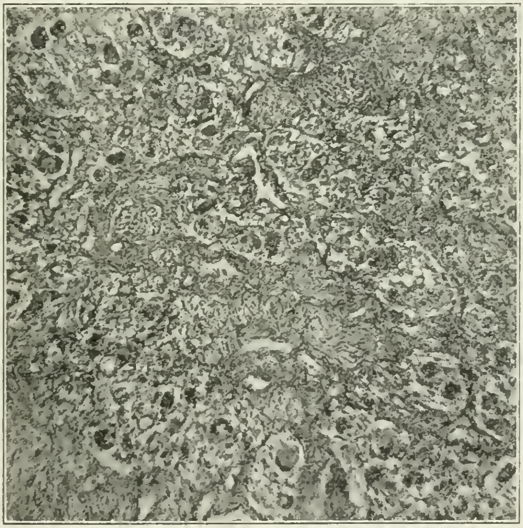

FIG. 6 (Case 11).—Section of left superior cervical sympathetic ganglion, silver impregnation, 10 microns, × 120 diameters. Marked reduction in the number of cells, many normal, and many in varying stages of advanced degeneration; marked increase of fibrous connective tissue.

CASE 11 (A156,404).—The patient, a female, fifty-five years of age, had had thyroid enlargement for twenty-four years. A thyroidectomy of the right lobe was done six years before, followed by a remission of all symptoms until a recent onset of cardiac distress. At the time of examination she had lost weight from 150 to 135 pounds; had a systolic blood-pressure of 158, and a diastolic of 88. The left lobe of the thyroid was extirpated and the internal jugular on the left side ligated. The patient died three days after operation. At autopsy, two hours and thirty minutes after death, the macroscopic findings were marked acute edema of the glottis, moderate hypertrophy of the myocardium of the left ventricle, marked disseminated nodular thickening of the aorta and of the aortic and mitral valve leaflets, and a moderate sclerosis of the coronary arteries.

Microscopically, the thyroid showed advanced regression of a moderate hypertrophy and hyperplasia, with considerable adenomatosis, Type C–3[7]. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Of the cells present, many were normal, but a large number were in varying stages of advanced regeneration. There was marked increase of fibrous connective-tissue in the ganglia (Fig. 6).

Summary of Protocols.

A study of the preceding protocols shows that of the 11 patients, 7 were females between nineteen and thirty-nine years of age and 4 were females between forty-eight and fifty-five years of age.

When considered in relation to the duration and stage of the symptoms of exophthalmic goiter the cases may be roughly grouped into three classes:

A. Cases still presenting active progressive symptoms of hyperplastic toxic (exophthalmic) goiter. These are as follows:

1. (A156,845) Female, aged nineteen years, symptoms five months, severity 3.*

2. (A153,535) Female, aged nineteen years, symptoms five months, severity 2 to 3.

3. (A136,418) Female, aged twenty-five years, symptoms two years, severity 3.

4. (A144,809) Female, aged thirty years, symptoms eight months, severity 3.

B. Cases in which the severity of the symptoms of hyperplastic toxic goiter had partially subsided, though the acute toxic condition was yet present. These are as follows:

5. (A11,264) Female, aged thirty-three years, symptoms two years, present severity 2.

6. (A149,095) Female, aged twenty-eight years, symptoms six years, severity 3.

C. Cases in which the acute toxic symptoms had almost, if not completely, subsided. These are as follows:

7. (A135,172) Female, aged thirty-nine years, goiter for sixteen years, maximum severity four years ago 3, present severity 1.

8. (A109,170) Female, aged forty-eight years, goiter four years, symptoms five years, present severity 1.

9. (A147,479) Female, aged forty-nine years, goiter thirty-two years, symptoms for two years, present severity 1 to 2.

10. (A67,759) Female, aged fifty years, goiter for twenty years, symptoms during first three years of goiter, then remission until during last six months, present severity 1.

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* On a scale of 1 to 5, in which 5 represents the greatest severity.

11. (A156,404) Female, aged fifty-five years, goiter twenty-four years, thyroidectomy right lobe six years ago for doubtful exophthalmic goiter, remission until recent onset of cardiac distress.

The first 4 cases may be grouped with 5 others previously reported[1] in which only the ganglia removed at operation were examined. In these 9 cases of acute progressive hyperplastic toxic goiter, there was very marked hyperpigmentation with extentive granular degeneration, and in some cases atrophy of the ganglion cells.

Cases 5 and 6 may be grouped with three operative cases previously reported.[1] These 5 cases showed considerable hyperpigmentation and granular degeneration, though a smaller number of cells were involved than in the ganglia from the cases of the first group.

Cases 7, 8, 9, 10, and 11 may be grouped with 6 other previously reported[1] operative cases. These 11 cases all showed a very marked regression or complete absence of toxic symptoms at the time of operation or death. In the ganglia from all of these the hyperpigmentation and granular degeneration affected a relatively small percentage of the cells present. In many of the cases, however, a marked diminution in the total number of cells present in the ganglion was shown by sections in series including the entire ganglion.

DISCUSSION.

Thus it will be seen that roughly the degree of hyperpigmentation, the amount of granular degeneration, the atrophy and the reduction in the number of cells was in direct relation to the continuation and subsequent remission of the symptoms of hyperthyroidism. Parallel with this, the perivascular connective-tissue and the connective-tissue stroma generally throughout the gland was increased in direct ratio to the time during which the symptoms of hyperthyroidism had continued. In two of the cases there was marked sclerosis of the ganglionic connective tissue.

Though the present number of cases is too small from which to draw positive conclusions, the observations so far seem to indicate that early in acute hyperplastic toxic goiter there is present in the superior cervical, and probably also in some degree in the other sympathetic ganglia, a process which is causing active stimulation, overfunction, and progressive stages of degeneration in the ganglionic cells. As the symptoms of exophthalmic goiter regress, evidence is found in the ganglia of the cessation of this degenerative process in the ganglionic cells not previously changed past recovery. After the acute toxic symptoms have entirely ceased for years, there remains little evidence of the destroyed ganglionic cells, most of the fatty pigmentary remains of the cells apparently having been absorbed.

The problems of the pathologic changes in the sympathetic ganglia in man have been obscured in the past by the occasional presence of pigment in the ganglion cells from patients who had exhibited no symptoms of involvement of the sympathetic system. Normally, the cells of the sympathetic ganglia in man are relatively free from pigment until adult life. They then may acquire more or less extensive deposits of brown pigment granules, arranged crescentically about the nuclei. The ganglion cells of patients dying of prolonged wasting diseases, such as tuberculosis and cancer, are apt to show an increased amount of pigmentation and in some instances varying stages of degeneration, hyperchromatization, chromatolysis, and granular degeneration. As control material in these respects many ganglia have been studied by methods parallel to those used on the ganglia from the goiter cases.

CONTROLS.

The control autopsy material is as follows:

1. (A139,228) Eight months' fetus. Placenta previa; atelectasis. Ganglionic cells normal; no pigmentation.
2. (A138,548) Eight months' infant. Pneumonia, following operation for hare lip. Ganglionic cells normal; no pigmentation.
3. (A149,999) Female, aged seventeen years. Pituitary tumor. Death following puncture of corpus callosum. Dilatation of heart; acute nephritis; fatty liver. The lymph spaces around the ganglionic cells are much dilated; the cells are shrunken and hyperchromatic, but not pigmented nor degenerated.
4. (A139,228) Female, aged thirty-six years. Placenta previa; mother of fetus Case 1. Normal; no pigmentation nor degeneration of the cells of the cervical ganglia.
5. (P. B. H. No. 61) Male, aged thirty-four years. Acromegaly; colloid goiter. No pigmentation and no degeneration in ganglia found.
6. (A149,288) Male, aged thirty-five years. Congenital cystic kidneys; hematuria. Some pigmentation, but no degeneration of the ganglionic cells.
7. (38 P. B. H. 3289) Male, aged thirty-eight years. Acromegaly. Some hyperchromatolysis and hyperpigmentation; no granular degeneration of cells found.
8. (A136,199) Male, aged fifty-two years. Carcinoma of anterior wall of stomach; acute parenchymatous nephritis. Autopsy five hours after death. Considerable pigmentation of ganglion cells; no degeneration.
9. (A134,342) Male, aged sixty-four years. Carcinoma of stomach; coronary sclerosis; myocarditis; chronic nephritis. Pericellular lymph spaces of ganglia dilated; cells shrunken; feeble staining; little pigmentation; no degeneration.

The operative control material consists of gasserian ganglia removed from six patients with trifacial neuralgia in the Mayo Clinic, and from one patient in the Peter Bent Brigham Hospital, and one cervical sympathetic ganglion removed in the Mayo Clinic because of its apparent involvement in a male patient fifty years of age in whom the primary lesion had been a persistent branchial cyst. Although the gasserian ganglia in the 6 cases of trifacial neuralgia and the cervical sympathetic in the branchial cyst case, were all the subject of ganglionic or periganglionic chronic inflammatory changes, and although the patients were from forty-one to seventy-one years of age, in none of the ganglia was there found evidence of such extensive degeneration of the ganglion cells as in the cases of exophthalmic goiter. In all the cases, there was more or less increase of pigment over that found in the ganglia of young adults, but in no case was the amount comparable with that found in exophthalmic goiter cases. Destruction of the ganglionic cells was apparently absent.

Thus it is suggested that neither advanced age, chronic wasting disease, nor chronic inflammatory processes necessarily cause degenerative changes in the sympathetic ganglia resembling those in exophthalmic goiter.

Involvement of Other Ganglia.

The question is suggested whether the involvement of the superior and middle cervical sympathetic ganglia in exophthalmic goiter is but a part of a general metabolic disturbance evidenced by similar changes in the sympathetic ganglia elsewhere in the body, or whether it is confined to the cervical sympathetic ganglia alone. In only 4 cases in which the cervical sympathetic ganglia were shown to be involved have we been able to study the ganglia from other portions of the body. In none of these was there positive evidence of involvement other than hyperpigmentation. There was little or no granular degeneration present resembling that found in the middle and superior cervical sympathetic ganglia. These observations will, of course, need to be confirmed by a much larger series of cases, but they suggest that the ganglionic changes in exophthalmic goiter may be confined largely to the cervical sympathetics, and that they may not be a secondary result of a general metabolic disturbance.

Experimental Work.

With a view to determining the possible relationship of the lesions in the sympathetic ganglia to exophthalmic goiter, studies have been made of the ganglia in a number of animals (dogs, goats, spermophiles, rabbits, and monkeys), in some of which many of the symptoms of exophthalmic goiter had been produced by the administration of Kendall's[6] alpha-iodin compound, in others which had been subjected previously to double thyroidectomy, and in others in which the cervical ganglia had been injected with various bacteria. In only one animal, however, were suggestive degenerative changes found in the ganglionic cells. In this animal, a young male goat, a small amount of a virulent broth culture of *Bacillus bronchisepticus* (the bacillus associated with canine distemper, and an organism which frequently affects the central nervous system), was injected into the right superior cervical ganglion. The animal died twenty-four days later, and necropsy was performed within an hour after death. The superior cervical sympathetic ganglion from the left side and the stellates from both sides were all apparently normal. The right superior cervical sympathetic, which had received the injection, showed at the immediate site of the injection a small area in which the ganglionic cells were completely destroyed and replaced by necrotic tissue. Throughout the remainder of the ganglion the cells were highly pigmented and showed various degrees of advanced degeneration. In fact, the lesions were quite parallel with those in the cervical ganglia removed from patients with acute exophthalmic goiter.

These experiments are being repeated, and will be made the subject of a subsequent report.

In conclusion, I wish to thank Professors Wm. T. Councilman, Harvey Cushing, and Walter B. Cannon, of Harvard Medical School, for kindly permitting me to examine their ganglionic material from autopsies, operations, and animal experiments.

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THE ETIOLOGY OF PELLAGRA: A CONSIDERATION OF VITAMIN DEFICIENCY.[1]

By Edward J. Wood, M.D.,
WILMINGTON, NORTH CAROLINA.

In a previous communication[2] it was suggested that the relation of corn to pellagra was analogous to the relation of rice to beriberi. The object of the present study was to determine the results of feeding chickens and pigeons on the offal of the corn mill (which is known as corn chops) after the development of symptoms produced by feeding deficient corn products. The second portion of the work has to do with the application of the information obtained by animal experimentation in the treatment of pellagra in man. Soon after starting the present work it became apparent that the milling and cooking of wheat products played an equally important part in the production of vitamin deficiency.

It had been shown by John M. Little[3] that deficient wheat flour caused a form of polyneuritis in man which must be counted true beriberi. W. R. Ohler,[4] prompted by a suggestion from Little, did extensive experimentation and produced the same type of polyneuritis by feeding chickens hominy as had been produced by deficient wheat. The result in both instances was the same as the type of polyneuritis produced with polished rice.

In 1914 Casimir Funk,[5] who had introduced into medicine the term vitamin, and who had seen his theory regarding the causation of beriberi and its remedy verified, suggested that there was the same relationship between the milling of corn and pellagra as had been proved between the milling of rice and beriberi. There was no experimental or clinical evidence presented, however, and the suggestion did not receive the attention it deserved, though the advocates of a deficiency cause never lost sight of the possibility of such a solution. Funk pointed out the marked difference in the composition of corn and of the germ of corn. The fat content of the whole grain is 5 per cent., while the germ contains 30 per cent. The loss of fat was thought by him to be a good indicator of the loss of vitamin, as there was evidence to show that the fatty portion contained the vitamin. South African and American corn were both deficient, but the latter more so because of the higher degree of milling. Funk was disposed to regard the mortality rate of the disease as an index of the degree of deficiency.

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[1] Presented at the meeting of the Association of American Physicians in Washington, May 10, 1916.

[2] Wood, E. J., Vitamin Solution of the Pellagra Problem, Jour. Am. Med. Assn., May 16, 1916, vol. lxvi.

[3] Jour. Am. Med. Assn., 1912, lviii and 1914, lxiii.

[4] Jour. Med. Research, vol. xxxi (new series, vol. xxvi).

[5] Prophylaxe u. Therapie der Pellagra im Lichte der Vitaminlehre, Munchen. med. Wchnschr., 1914.

It had been shown in the beriberi work that phosphorus pentoxide was a reliable indicator of vitamin, though there was no direct connection between the two. The same value is attached to it in the present work. Sulphur determination is being introduced by us as an aid in determining vitamin, but the work has not progressed far enough to justify any definite conclusions as to its value in comparison with the phosphorus indicator. So far the results obtained show a striking similarity.

Viewing pellagra as a deficiency disease, and attributing the deficiency to the milling process or to some chemical change which brings about destruction of vitamin in the process of cooking, it is no difficult matter to reconcile and even harmonize many of the views of the early Spanish, Italian, and French pellagrologers. The vast amount of literature which has accumulated since the publication of Casal's[6] original article has been very lifeless until recently. It now becomes reanimated by recent progress, and a careful study of this wealth of material is not only interesting, but of practical value, and we are filled with admiration at the keenness of the observation of those men who had so little opportunity for the accurate study of such a problem, and whose observations have stood so well the test of modern scientific advance. Sandwith[7] states that as early as 1707 Pedro Casal wrote in Spanish that pellagra was due to insufficiency of diet. In the latter part of the eighteenth century Franzago declared that maize was unhealthy only because it was an insufficient food, but he would not say it was the sole cause. Later, Marzari[8] claimed that the cause of the noxiousness of the corn was an insufficiency of gluten. Had there been a knowledge of Funk's theory of vitamin during that period in which corn was connected with pellagra in one way or another, the problem would probably have been solved long ago. The school of Lobroso had as a basis of its teachings a definite toxicity which may now be interpreted in terms of deficiency.

The germ of the corn lying at the hilus of the grain is poorly protected and subjected to the action of all injurious agencies both animal and vegetable. Damaged corn is always most affected in this part. Owing to the high fat content, the method of removing the germ before the grain was finally ground was introduced. This process was called "degermination." It is practised in many places and in many types of mill.[9] The two products of this form of milling are granulated corn meal and corn chops. The latter is spoken of as the offal of the corn mill and is sold as cattle food. In former times the grain was ground whole at the community water mill and there was no damage from the great heat which may be produced in rapid steam milling. This form of heat, however, is inconspicuous in comparison with the heating process which the grain often undergoes before reaching the mill.

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[6] Historia natural y medica de el Principado de Asturias. Abra posthuma del Doctor D. G. Casal, Medico de Su Magestad y su Protomedicin de Castilla, Madrid, 1762.

[7] Trans. Soc. Trop. Med. and Hyg., October, 1915.

[8] Essai Medico-politique, 1810.

[9] Farmer's Bulletin, 298, U. S. Dept. Agr.

The differences between corn chops and corn meal are given below:

	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Fiber, per cent.
Meal	9.2	1.9	74.4	1.0
Chops	9.0	7.0	70.0	9.0
Germ alone	21.7	29.6	44.7	
Endosperm	12.2	1.5	85.0	

Analysis of the various articles of food which were experimented with showed interesting variations in the P_2O_5 content. It was readily apparent that the cortex of the various grains, as has been formerly held, contained the bulk of phosphoric acid. It was also apparent that the amount was influenced by the degree of fineness of the product. Wheat middlings sifted in the laboratory with the removal of only the very smallest amount of bran showed a definite decrease in the phosphorus.

	P_2O_5, per cent.
Corn chops	1.15
Water-ground meal (North Carolina)	0.78
Whole meal, steam milled (Virginia)	0.60
Highly milled meal (Ohio)	0.29
Steam-milled meal (North Carolina)	0.58
Wheat middlings (offal of mill)	0.98
Whole-wheat flour	0.50
Average wheat flour (bought in Wilmington, North Carolina)	0.14

The first important suggestion of a vitamin deficiency caused by the milling process was made by P. A. Nightingale[10] in Rhodesia in 1912. He found that prisoners fed on highly milled meal developed a definite group of symptoms for which he coined the word "zeism," thinking it to be a new condition. There can be no doubt that this condition was acute pellagra, which has never been reported in medical literature except in the Southern States, in which it appeared in 1905. All references in European literature recognize pellagra only as a chronic process. Nightingale concluded that the use of highly milled meal had caused the disease, and substituted whole meal which was ground by hand in the jail. The result in his words was "immediate and magical."

Recent studies in polyneuritis gallinarum in its relation to beriberi now become of great value in suggesting a line of investigation in pellagra. Goldberger[11] has emphasized the importance of viewing pellagra in much the same light as beriberi, and we are indebted to him for the suggestion. It is not known that there is any connection between pellagra and beriberi, except that both diseases are probably deficiencies. Any experimental work in pellagra would, therefore, not be aided by a study of polyneuritis in fowl. The present work was undertaken to prove the fact that polyneuritis could be caused by meal made deficient in the milling process and cured by the portion of the grain removed in the production of the deficiency. Unexpected findings have thrown considerable light on the question, and have tended to suggest the possibility of a disease condition which seems to be due to a deficiency not so marked as to be sufficient to cause polyneuritis. It would seem that beriberi and pellagra, then, differ only in the degree of insufficiency.

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[10] Nightingale, P. A., Transvaal Med. Jour., 1912.

[11] Public Health Reports, June 24, September 11, October 23, 1914, Jour. Am. Med. Assn., October 10, 1914, and February 12, 1916, Public Health Reports, January 15, 1915.

The recent work of Voegtlin, Myers, and Sullivan[12] showed that vitamin was promptly destroyed by the use of soda and certain baking powders in the preparation of bread regardless of the original quality of the flour or meal. It was further shown that this could be prevented by the use of sour milk in conjunction with the alkali. Some baking powders contain enough tartaric acid to neutralize the sodium carbonate after the liberation of carbon dioxide. It is an interesting study to trace the introduction of this form of cooking and the appearance of pellagra, just as it is interesting to study the time connection between the introduction of highly milled meal and the disappearance of the old water mill which ground the corn *in toto*. In one community, at least, I have been able to show that the year which marked the abandonment of the old mill was the year of the appearance of the first cases of pellagra. Pellagra was unknown in the Confederate army, though lack of food was frequent; but there was no deprivation of the grains of any portion in the milling. There are broad areas in North Carolina in which pellagra has never occurred, though poverty and poor hygiene obtain in the fullest. These areas are separated from railroad travel, and home products are used through necessity. This is particularly true of the remote mountain counties. I have searched diligently through four such counties and have never been able to find the disease, nor could I learn of its occurrence from the physicians. But as the Piedmont section is reached and the people are able to procure manufactured products of every sort, the disease soon appears and reaches its high-point in the cotton-mill village, in which highly milled products are used almost exclusively and soda is added to every form of food to hasten the cooking (Voegtlin, Myers, and Sillivan).

Six pigeons were placed in a roomy cage outdoors with a floor to prevent the scratching of the earth. The best pigeon grit was abundantly supplied as well as plenty of fresh water. Whole corn was broken in the laboratory and allowed in great abundance. No other food was given throughout the experiment. For four months there were no developments of disease, though it was evident that conditions were not best suited for growth and development. At one time it was noted that there was some droopiness, and investigation showed that the corn used at the time was of an inferior quality. From that time seed corn was used. This group were the controls.

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[12] Public Health Reports, April 14, 1916.

In the second group of pigeons the food was corn meal with a P_2O_5 content of 0.58 per cent. After ten days it was noted that the pigeons had red legs in striking contrast to the controls, though of the same breed and age. In addition to the red legs there was marked droopiness and inactivity. After six weeks a more deficient meal with a P_2O_5 content of 0.29 per cent. was substituted. There was no change except increased redness of the legs. After these twelve weeks there had occurred only one death, and that from a cause having no bearing on the experiment. At this time it was decided to produce polyneuritis gallinarum if possible. Wellman and Bass[13] as well as Ohler had produced polyneuritis in less than three weeks on a diet better than the one in use by us. The most deficient meal was made into bread, with the addition of soda. After a month of this feeding there was still no polyneuritis. During the experiment two squabs had been hatched from eggs laid after the experiment had been several weeks under way. These squabs did very well until the time for them to feed themselves. In a very few days polyneuritis developed. By the administration of corn chops there was prompt relief. It is a notable fact that these young pigeons were the only victims of polyneuritis, though the diet was such that it was to be expected that none of the animals would escape. The successful feeding of corn chops proved for corn what had already been proved for rice and wheat. By alcoholic extraction a substance was found in the corn chops which was equally as effective as the alcoholic extract of rice polishings had been in former experiments.

It appeared that continued feeding of a gradually increasing deficiency diet resulted in the acquiring of a peculiar kind of tolerance which may later be shown to explain some of the peculiarities of pellagra. After red-legged pigeons had been kept on the same food for several weeks it was impossible to produce polyneuritis with the most deficient diet, and the red-legged condition was just as promptly relieved by feeding corn chops as was polyneuritis. Only a few days were required for a return to normal, though it was found that the longer the red-legged condition had existed the longer the time required for a complete subsidence.

Chickens hatched on the same day were divided into two groups.

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[13] Am. Jour. Trop. Dis. and Prev. Med., 1913.

One group was fed deficient corn meal while the control group was fed corn chops. The food of the deficiency group contained 0.58 per cent. P_2O_5 in the beginning, which was later replaced by a meal with a 0.29 percentage. The red-legged condition did not occur, but the chickens did poorly. There was one case of polyneuritis gallinarum which did not respond to treatment because discovered late. The growth in every case was below normal and droopiness was quite marked. At the end of the experiment the chickens fed on corn chops had gained 8 per cent. more than those on deficient food.

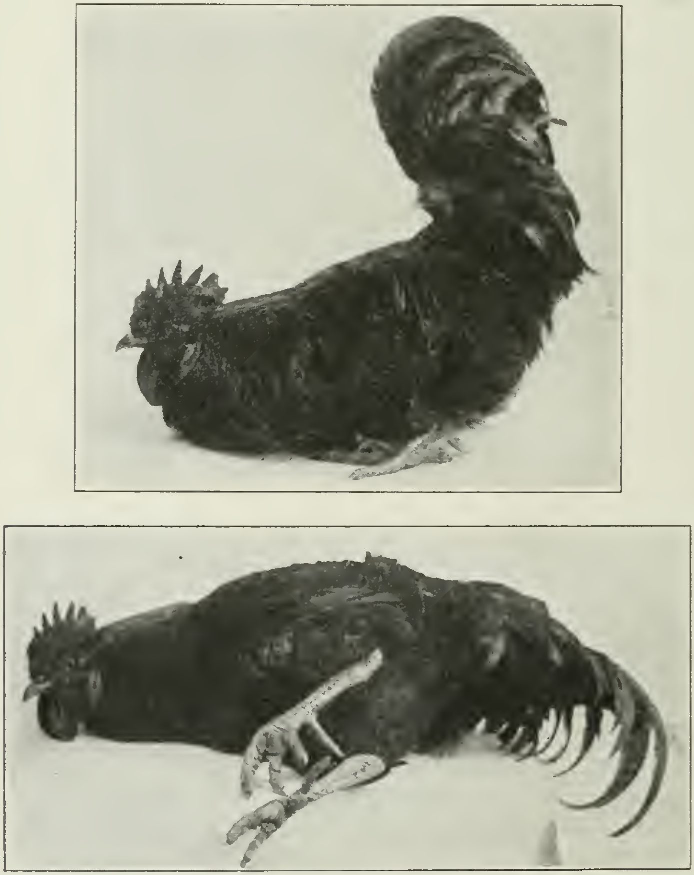

Fig. 1.—Photographs of a Rhode Island cock, showing complete paralysis: a definite case of polyneuritis gallinarum caused by feeding cooked hominy.

Through the courtesy of a colleague we were given the opportunity to study polyneuritis gallinarum in a Rhode Island Red cock. The cause was cooked hominy. The photographs show the extreme degree of paralysis and the prompt recovery after the administration of the extract of corn chops and a diet of the same food. This animal became neuritic by a change of diet which was not extreme, and at no time was there any confinement as in the experiments above recorded. The range was ample and the animal had abundant opportunity to supplement the hominy with other food. This suggests other factors not yet understood which play a part in deficiency conditions.

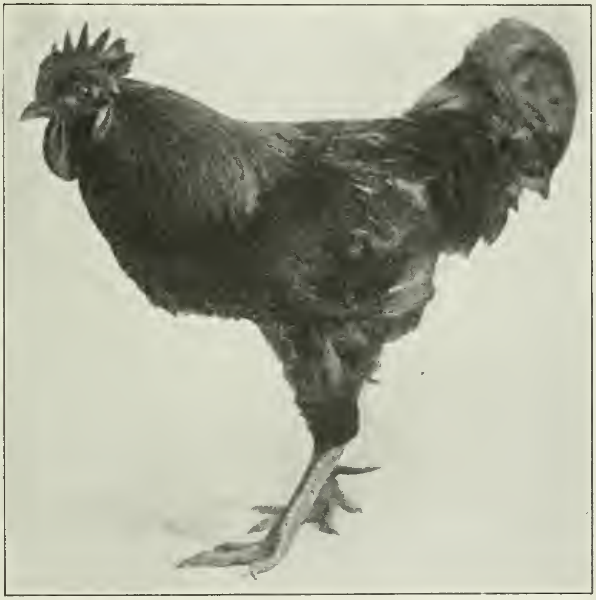

Fig. 2.—Photograph of the same cock forty-eight hours after feeding corn chops and the extract of corn chops. Improvement was immediate. Recovery was complete.

The red-legged condition was very definite and the cause was well established. The cure was equally simple. It would be beyond the scope of this work to attempt to show that the condition was analogous to pellagra as polyneuritis gallinarum is to beriberi. Suffice it to say that the observation was of the greatest help to us in our work, and by it we were able to determine very exactly the quality of the grain, for it was a very delicate indicator. We were disposed to regard polyneuritis as the result of a total deficiency and the red-legged condition as a partial deficiency. If this can be applied to pellagra it is readily understood why the coolie of the East has beriberi while in the South the deficiency disease is pellagra. The coolie eats one food and there is no chance for making up the deficiency with other foods. In the South there is always more than one food, and therefore the deficiency is made up in part at least.

Why it was impossible to produce polyneuritis gallinarum in the pigeons with the red-legged condition we cannot say. In several pellagrins we found polyneuritis which much resembled beriberi, though such a diagnosis was not ventured because of the frequency of the use of excessive dosage of arsenic in the disease. It is very probable that many cases of neuritis in pellagra have been caused in this way.

Feeling justified in the opinion that the portion of the grain removed in milling contained the vitamin, the lack of which caused pellagra, it was decided to feed pellagrins on exclusive diet of corn chops.

Case I.—A white man, aged sixty-five years. Symmetrical erythema of the backs of the hands, stomatitis, diarrhea, prostration, and emaciation. For several months the diarrhea had been troublesome, and the number of stools varied from six to ten in twenty-four hours. On Wednesday morning he was placed on an exclusive diet of corn chops, but allowed a little butter. The corn chops was baked as bread without soda or baking powder, and was also made into a gruel. The patient was fed five times during the day. It was explained to him that the remedy was in the food and could not be successfully extracted. After forty-eight hours the relief was most striking: the diarrhea had ceased, the stomatitis was relieved, and desquamation was progressing rapidly. On Sunday he was discharged, with only the one complaint, constipation, to be considered. He was kept under observation for several weeks in the dispensary, and there occurred no recurrence.

Case II.—A white man, aged fifty-six years. The backs of his hands were covered with a bullous erythema and the redness was intense. The first physician who saw him suspected a dangerous skin infection. The lesions were perfectly symmetrical. There was a complaint of stomatitis and diarrhea. In addition the patient was a diabetic. He was placed on a diet of corn chops, and at the end of four days the skin lesions were relieved and exfoliation was progressing rapidly, the diarrhea and all other symptoms had ceased. After a few days he was given the Allen fast and treated for the diabetes, with prompt disappearance of sugar. After three months there has occurred no recurrence of pellagra.

Case III.—A well-conditioned white woman, aged twenty-two years. She had many peculiarities of diet, and as a result was suffering from pellagra of a typical type. The erythema covered the backs of her forearms, and there was a classic Casal collar. She complained of diarrhea and stomatitis. After four days of corn chops she was relieved of all symptoms, and at the end of a week desquamation was complete. After two weeks of this treatment she had gained eight pounds and felt better than in years. She was allowed other things besides the chops, but was required to eat the latter at least three times a day.

It was found that far-advanced cases were not relieved in this striking manner, though improvement often followed, and the treatment was well justified. After a time structural change takes place both in the intestinal tract and the nervous system, and no treatment can avail anything. This is equally true of other diseases for which there are specifics.

Case IV.—A negro woman, aged about thirty years, was admitted to the hospital in a hopeless condition. She was far advanced in dementia. The bowels and bladder were being emptied in the bed, and the patient required an attendant constantly to keep her in bed. It was impossible to feed her except by the tube, which was used three times in the twenty-four hours. At each feeding a pint of milk and three eggs were given. There was some improvement, but it was not marked until four ounces of a gruel of wheat middlings was added. The intestinal condition improved promptly, and there would be periods of entire freedom from the diarrhea. The mental condition also improved, and the use of the tube was abandoned. The patient died rather suddenly from an unknown cause. In spite of the unfavorable termination there could be no doubt that the food caused improvement, and more markedly when the food containing grain cortex was added.

In all cases treated by the feeding method no drugs were used except an occasional placebo. It was soon learned that the corn chops to be effective must be freely milled. Just how this can be worked out practically remains to be demonstrated by some reliable dealer. Whatever the essential substance is there can be no doubt that it is very unstable, and apart from this, owing to the occurrence of rancidity, corn chops keeps very poorly. Some chemical process may be introduced to extract from the corn chops or the wheat middlings the essential substance. Our own efforts along this line, while proving that such a substance was present and could be extracted, were too expensive for practical purposes because of the great amount of alcohol necessary. Mr. G. F. Catlett was able to secure 65 c.c. of a watery substance from one kilo of corn chops by extracting with 8000 c.c. of 95 per cent. grain alcohol. The same general plan was followed as had been formerly used in the preparation of rice polish extract. The product made in our laboratory from corn chops was certainly as effective as rice polish in polyneuritis gallinarum when that condition was caused by defective corn. There is no reason to believe that it would not have been equally as effective if the polyneuritis had been caused by polished rice. Certainly in pellagra we were able to relieve the symptoms by the use of wheat middlings in one case and corn chops in others. This suggests that there probably is no specificity in the vitamin, but that all grains under discussion yield a certain amount, and that the only difference is one of richness.

While the bulk of our experimental work was confined to a consideration of corn deficiency, we are entirely in accord with those observers who regard the wheat as a more frequent source of the deficiency in the South at this time. We were in a position to study the corn question, and were desirous of explaining in the beginning why polenta, the national dish of the Italian peasantry, caused pellagra. It can be readily accepted now that the toxicity of Lombroso was really a deficiency, and that the food forming almost the exclusive diet of the people under his observation was polenta. Polenta is a thick corn-meal mush, which was kept for days after its cooking, and which usually underwent fermentation. It has been shown that when corn is deficient the germ is usually the portion of the grain first and most seriously damaged regardless of the source of injury. Much of this Italian corn was badly damaged, and therefore was deficient because the vitamin had been destroyed in the germ. We will later study the result of fermentation on the vitamin content of polenta.

It is obvious that vitamin deficiency of the grain food may be replaced by an abundant protein diet of fresh lean meat, fresh milk, eggs, and various other expensive foods. It is also obvious that an infant may be protected from scurvy while on a faulty diet by giving such an antiscorbutic as orange juice. But is there justification for such a procedure? With the gradually increasing cost of foods of the vitamin supplying type, the poor whites of the South are no nearer their salvation from this great scourge. Lombroso once said that it would be equally as effective to advise his patient to be rich as to advise the diet needed, and if the patient were rich he would not have to be advised about the diet, for his natural desires would protect him from the disease. If decortication of grain and faulty methods of cooking cause the disease, the remedy is not beyond the reach of the poorest pellagrin. And this is our experience. It is, of course, granted that the high protein diet is most desirable, but the practical solution of the pellagra problem in the South calls for some other remedy. It can be easily shown that people live without meat, milk, eggs, and other expensive protein, and still do not suffer from pellagra. Our experience is that such people do not eat decorticated grains. We have also learned, as pointed out on a previous page, that the response from feeding pellagrins the decorticated portions of the grain is more prompt than when the diet is meat and eggs. It is to be hoped that the vitamin preparation of A. Seidel,[14] which is prepared from brewer's yeast, using Lloyd's reagent, will be an inexpensive source of making up the deficit in the diet of the pellagra class. We have had no opportunity to test it in the treatment of the disease.

It would appear to us that pellagra is readily prevented; that the prevention does not require any increased cost of living; that the use of whole grains that have not undergone destructive changes and the avoidance of alkaline rising agents would entirely eradicate the disease.

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[14] Public Health Reports, 1916.

It gives me pleasure to acknowledge my debt to Mr. G. F. Catlett, who by his sympathetic advice and aid in the chemical portion of this study has made it possible.

SALVARSAN IN THE TREATMENT OF DOUBLE INFECTIONS, TUBERCULOSIS, AND SYPHILIS.[1]

By Nathaniel Bowditch Potter, M.D.,

PROFESSOR OF CLINICAL MEDICINE, COLUMBIA UNIVERSITY, COLLEGE OF PHYSICIANS AND SURGEONS; VISITING PHYSICIAN TO THE NEW YORK CITY HOSPITAL; CHIEF OF MEDICAL DIVISION OF ST. MARK'S HOSPITAL; CONSULTING PHYSICIAN TO THE FRENCH HOSPITAL, TO THE NEW YORK THROAT, NOSE AND LUNG HOSPITAL, AND TO THE CENTRAL ISLIP STATE HOSPITAL.

The universal employment of the Wassermann reaction has revealed the striking frequency of an unknown or an unacknowledged syphilitic infection in patients with tuberculosis. The greater participation of careful internists in the problems of lues and the development of more recently devised tests have been responsible for showing that either as a result of their disease, or of its vigorous treatment, syphilitics exhibit an increased susceptibility to tuberculosis. Recent experience with the late lamented Paul Ehrlich's epoch-making drug, salvarsan, promises hope for the future in the treatment of patients afflicted with these combined infections, and very likely the diminution of syphilitics' susceptibility to the great white plague.

In ten years of prison service, Tedeschi[2] found that 70 per cent. of the cases of pulmonary tuberculosis had developed upon a luetic soil.

Among 346 tuberculous inmates of Boucicaut Hospital, 19 per cent. (64) gave a positive Wassermann reaction, although but 3 per cent. (10) acknowledged a previous luetic infection or showed any signs of it.[3] Among 116 patients at Brompton Hospital with pulmonary tuberculosis selected at random by Inman,[4] he found only 5 per cent. (6) positive. The admissions to a children's orthopedic hospital in Sweden[5] during three years included 29 affections of the knee, of which 20.7 per cent. were non-tuberculous while two-thirds of this percentage were plainly luetic, with a positive Wassermann reaction. This test was also positive in many other cases at the hospital, and in a large number with unmistakable tuberculous lesions, and for the most part in children with latent syphilis (in reality inherited lues), although called "scrofula." Among 22 more recent admissions to the same hospital, all of whom were recommended with the diagnosis of some form of tuberculosis, 23 per cent. (5) showed a positive Wassermann reaction.

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[1] Read by title before the clinical section at the Eleventh Annual Meeting of the National Association for the Study and Prevention of Tuberculosis, held at Seattle June 14 to 16, 1915, but not completed in time for publication in the Transactions.

[2] Studium, Napoli, 1910, iii, 343, 377.

[3] Bull. Acad. de méd., Paris, 1914, Series 3, lxxi, 596. (Abst.) Jour. Am. Med. Assn., Chicago, 1914, lxii, 1848.

[4] Compt. rend. Soc. de biol., Paris, 1914, lxxvi, 254.

[5] Norsk. Mag. f. Laegevidensk, Christiania, 1915, lxxvi, 557–696. (Abst.) Jour. Am. Med. Assn., 1915, lxiv, 2030.

Among 47 patients with lues at various stages of the disease tested with tuberculin by the intradermic method of Mantoux, 94 per cent. (44) showed a strongly positive, 4 per cent. (2) a doubtful, and 2 per cent. (1) a negative response; while in 28 of these cases a von Pirquet test showed 75 per cent. (21) positive, 14 per cent. (4) doubtful, and 11 per cent. (3) negative reactions.[6] In comparing these figures with the ones Mantoux himself obtained in 91 cases of known tuberculosis (81 positive reactions, or 89 per cent.; 3 negative, or 3 per cent.) the observers concluded there was too slight a difference to be of striking diagnostic value; but called attention to the more intense and persistent intradermic reaction to tuberculin in the syphilitic patients than in those in whom tuberculosis alone existed.

Bronfenbrenner's[7] recent experience with the complement-deviation test, employing Besredka's tuberculin, indicates that the incidence of tuberculosis is very much higher among syphilitics than among non-syphilitics, and probably because lues itself or antiluetic treatment markedly lowers the resistance, and so renders such individuals either more susceptible to the acquisition of or less resistant against the awakening or progress of a previously contracted tuberculosis.

Numerous articles and reports of cases more and more accurately studied from the clinical, therapeutic, bacteriological, pathological, and recently from the radiographic and serological point of view have clarified our conception of uncomplicated pulmonary lues, and lessened the difficulties in respect to both the diagnosis and the treatment of co-existing luetic and tuberculous pulmonary infections.[8] Stengel[9] carefully analyzed the more authoritative literature upon pulmonary syphilis, and suggested that the discrepancy in the published statements of the frequency of acquired, as contrasted with hereditary lues of the lung, depended upon whether the author was a clinician or a pathologist; the former, accepting the accuracy of such a diagnosis upon insufficient evidence, and the latter, aided only by the old histological methods, excluding many a suggestive case if studied in accord with modern technic.

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[6] Nicolas, Favre, and Charlet, Lyon méd., 1910, cxiv, 624.

[7] Arch. Int. Med., Chicago, 1914, xiv, 786.

[8] Am. Jour. Med. Sc., Philadelphia, 1905, cxxix, 563. New York Med. Jour., 1913, xcviii, 600. Councilman's papers quoted Johns Hopkins Hosp. Bull., Baltimore, 1891, ii, 34. Med. Contemp., Lisb., 1912, xxx (Abst.), Jour. Am. Med. Assn., 1912, lix, 1932. Hosp. Tid., Copenhagen, 1914, lvii, 321–352. (Abst.) Jour. Am. Med. Assn., 1914, lxii, 1370. Rev. gén de clin. et de thérap., Paris, 1914, xxviii, 86.

[9] Univ. Penn. Med. Bull., Philadelphia, 1903–1904, xvi, 89.

A wave of therapeutic enthusiasm for mercury and even for the iodides engulfed many clinicians and institutions devoted to the care of tuberculous patients in the nineties, and, as was natural, some good but much harm was done.[10] With evidence of a previously acquired, or an inherited syphilitic infection a beneficial effect from one or both these remedies is readily understood and should be expected;[11] but there is no convincing proof that any benefit will result from the use of mercury or iodide of potash in the tuberculous who are not at the same time luetic. There is, on the contrary, much evidence of danger attending the vigorous use of these drugs, especially of mercury[12] in tuberculous patients with a tendency to hemoptysis, and of the iodides, as a result of their congestive effect.

Although Ehrlich[13] originally included advanced cases of tuberculosis among the contra-indications to the use of salvarsan, subsequent clinical reports show that with care such individuals need not be deprived of the assistance afforded by the new remedy.

Herxheimer and Schonnefeld[14] first reported the use of salvarsan in a luetic patient with pulmonary tuberculosis. After a four weeks' course of intensive mixed treatment had failed to modify the testicular lesion of a patient plainly infected with both diseases, salvarsan (0.5) was given. The resulting benefit was immediate and striking, but no details of its effect, if any, upon his double apical pulmonary lesion were cited. Treupel[15] described an advanced case of pulmonary tuberculosis in a physician, aged thirty-three years, in whom the faithful and vigorous use of mercury inunctions had not cured a luetic infection of a year's duration. Intramuscular injection of salvarsan (0.6) produced quite a severe reaction at the bilateral sites of inoculation; and at first considerably upset the patient, with a maximum temperature of 38.5° on the second day. The writer noted the beneficial effect upon the symptoms referable to syphilis, and stated that the pulmonary condition was unchanged. Gluck[16] cites a serious case of malignant syphilis with fever and with a pulmonary catarrh very favorably influenced by one injection of salvarsan (0.4), but gives no details about the lung condition before or after treatment.

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[10] Wien. Klin., 1895, xxi, 259.

[11] New York Med. Jour., 1908, xxxviii, 385.

[12] Jour. Am. Med. Assn., Chicago, 1910, lv, 915.

[13] Abhandlungen über Salvarsan, J. F. Lehmann, München, 1911, i, p. 391; 1912, ii, p. 554.

[14] Med. Klin., 1910, vi, 1400.

[15] Deutsch. med. Wchnschr., 1910, xxxvi, 1393.

[16] München. med. Wchnschr., 1910, lvii, 1638.

In an analysis of 375 cases treated with salvarsan, Sieskind[17] states that he has treated patients with hemoptysis and with phthisis in varied stages without ill effect, and always with general improvement and an increase in weight. Among the indications for its use he includes luetic patients with tuberculosis, in whom mercury affects the tuberculosis adversely. Treupel and Levi[18] state that they have injected salvarsan into syphilitic patients with open pulmonary tuberculosis without unfavorable effects on the latter disease, except possibly in two cases: one a patient with an old apical tuberculous process in whom an intramuscular injection was followed three weeks later by temperature and an exudative pleurisy; and another who developed a croupous pneumonia upon the same side as and two weeks after an interscapular injection, which had been followed by an extensive and persisting deep infiltration. Herxheimer and Altmann[19] administered salvarsan to 9 patients with glandular, cutaneous and pulmonary tuberculosis (and also experimentally to animals), and called special attention to the resulting focal reaction, apparently identical with that produced by injections of tuberculin. Although they selected only small doses no beneficial effect upon the tuberculous process was detected. In 4 cases of lupus this focal reaction was especially well studied: it consisted of pain, heat, swelling, and redness, appeared within four to six hours after the injection, lasted about twenty-four hours, disappeared with scaling, and its intensity apparently ran parallel to the degree of the disease. Reinjection produced a less vivid effect. No benefit was noted in the skin lesion in 3 of the cases after three injections following each other within three or four weeks. They compared it to the so-called Herxheimer's reaction and liken it to a mobilization of tuberculin. In a patient with secondary lues and tuberculous cervical glands the administration of salvarsan (0.5) was followed by a focal reaction with subsequent softening and pus formation (bacilli positive), necessitating a later operation. In two of their patients with pulmonary tuberculosis the second dose of salvarsan was followed by a general as well as a focal reaction (cough and rales). A fourth patient with a healed apical process developed a local, focal, and general reaction five days after the injection of salvarsan (0.5) into the gluteal region, and showed at autopsy an induration and encapsulated caseation in the lungs; but the cause of the sudden death was a pulmonary embolus from a thrombus in the femoral vein, secondary to a streptococcus abscess at the site of inoculation, and had nothing to do with the coexistence of tuberculosis. Bine[20] gave salvarsan to a patient with glandular tuberculosis and a positive Wassermann, but his report does not mention the results. Fordyce so treated Harris's[21] patient with pulmonary tuberculosis and tertiary lues (extensive nasal necrosis) with an excellent effect upon the latter disease; but neither details of the physical examination of the chest nor the effect of the medication upon the former disease are available, and the patient cannot be traced. Despite the coexistence of an apical catarrh, 2 of Schiele's[22] patients with tertiary lues derived benefit from the intramuscular injection of salvarsan (to one 0.3 twice to the other 0.5). Although the condition of his third patient scarcely justified resorting to salvarsan (0.3 lumbar) and was followed by a rather severe reaction, her subsequent marked improvement and the elapse of two and a half months before she died, render decision rather difficult as to the responsibility of the drug. The dose, however, was larger than would be selected today. This patient was aged twenty-nine years, under-developed, poorly nourished, deaf, with hereditary lues of a progressive type, with double apical consolidation, bronchial breathing at one apex and severe cough, with a large hard liver, an enlarged spleen, a tender, painful, resistant abdomen, copious diarrhea, a perforation of the hard palate, a negative Wassermann, and with a still unhealed sinus from an operation upon one mastoid nine months previously. She died after a recurrence of diarrhea and severe abdominal pain. Jacquet[23] administered salvarsan, 0.6 (intragluteal), to a male, aged forty-two years with pulmonary tuberculosis of the second stage, left pleurisy, luetic lesions of foot soles, testicle and epididymis, and a positive Wassermann. Although not known at the time of inoculation the patient had had an hemoptysis a short time before. The effect of the treatment was strikingly good upon the luetic process, the general condition, and even upon the active pulmonary signs. In addition to the 2 fatal cases cited above (Herxheimer and Altmann, Schiele) Wechelmann's[24] collection of deaths following the use of salvarsan includes 10 others, exhibiting clinical or postmortem evidence of the existence of both tuberculosis and lues. The existence of the former evidently had nothing to do with the effect of the drug or with the fatal termination in 5 of them. If his meager details can be relied upon for judgment, neither of Dind's 2 cases were in a condition to justify the use of salvarsan, although the one with pulmonary and meningeal tuberculosis, admitted in coma and injected only as a last resort, was given but 0.1. Schlasberg's case with tertiary lues had phthisis and also chronic nephritis, and was given salvarsan (0.4) about twelve weeks after a course of seven injections of mercury, which had not been well tolerated. Autopsy, however, pointed to nephritis as the cause of death. Vorner's[25] fatal case, with the history of lues dating back twenty, and of tabes ten years, was given salvarsan (0.6), followed within twenty-four hours by a chill, fever, rapid pulse, headache, nausea, and vomiting; the urine contained 1 per cent. albumin, the temperature persisted for six days, and the patient continued to be nauseated and very weak for about seven days; at the middle of the second week, insomnia and further exhaustion; at the fourth week, condition more serious, afternoon fever, nausea, a painful tender rigid abdomen, diarrhea, enlarged liver, increasing exhaustion, and death. Autopsy disclosed a general miliary peritoneal tuberculosis and enlarged softened mediastinal glands, histologically tuberculous. The author attributes the result to a hyperemia of the glands and a proliferation of the tubercle bacilli; likens it to a Herxheimer reaction, and claims that salvarsan is liable to activate any latent infection, including tuberculosis. Despite his statement that the physical examination revealed nothing noticeable about the internal organs, no such advanced and extensive tuberculous lesions as were disclosed at autopsy could have developed within five weeks of the injection of salvarsan; and his selection of so large a dose for a patient in such a wretched condition was, in view of our present experience, injudicious. The internal organs were also recorded as normal in the physical examinations of two of Finger's fatal cases; in both of which a chronic glandular tuberculosis was disclosed at autopsy to be the source of the active fresh lesions at the base of the brain and elsewhere. To one of them a second dose (0.4) was administered, despite a warning reaction after the first injection and the persistence of headache; and to the other, even a third dose (0.4), although after a long interval; but despite the warning of a Herxheimer reaction which followed the first dose; and the patient's complaint, at the time of the final injection, of severe pains in ears, headache, and malaise. These three fatalities suggest more care in preliminary examination and the selection of smaller doses. Wechselmann urges a carefully studied spinal puncture before administering salvarsan to tuberculous patients complaining of headache. Audry[26] gave arsenobenzol (0.3) to an anemic woman, aged twenty-six years, who had a tuberculous involvement of one apex, and who, six years previously, had shown symptoms of and had received some treatment against an unacknowledged luetic infection. Decided improvement in both diseases followed, but a second dose (0.3), administered seven months later on account of a recurrence of specific cutaneous symptoms, was followed by vomiting, an increase in the cough and considerable bloody sputum. The latter disappeared after three days, but no alteration in the pulmonary signs could be detected. McDuffie[27] gave salvarsan to hopeless cases of tuberculosis, but his report lacks all details. Robinson[28] found that an injection of salvarsan (0.4) to a patient with pulmonary tuberculosis and lues was followed by a rapid decrease in the amount of sputum; and that (0.6) produced no ill effect upon the tuberculous lesion in another patient who exhibited an active process and who became infected with syphilis. In 9 patients with different stages of tuberculosis, Courmont and Durand[29] tested the effect of Billon's arsenobenzol, administered in the form of enemas (eight doses twice a week of 0.1 in 5 c.c. of warm saline, properly alkalinized). Two of these patients were also luetic: one, a tabetic, aged forty-three years, with extensive fibrocaseous tuberculosis, in whom the treatment seemed to aggravate the pulmonary condition and diminish his weight, although his pains were alleviated; the other, but without bacilli in the sputum, with a chronic fibrous consolidation at one apex, and the history of numerous attacks of pleurisy was much benefited. Robin[30] commends the recent abandonment of mercury in favor of salvarsan for patients with co-existing lues and tuberculosis, and especially if a tuberculous patient becomes infected with syphilis and whenever the latter disease takes a grave course. He cites the case of a male, aged thirty-three years, with a tuberculous family history and evident signs of chronic fibroid tuberculosis since the age of twenty. For three years past some signs of activity, quickly relieved by rest. He contracted syphilis eight months ago, was very inadequately treated with mercury benzoate. His pulmonary signs and symptoms rapidly increased and to secure a prompt action he was given three successive doses of salvarsan with excellent results.

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[17] München med. Wchnschr., 1910, lvii, 2027.

[18] Ibid., 1911, lviii, 237, 305.

[19] Deutsch. med. Wchnschr., 1911, xxxvii, 441. Arch. f. Dermat. u. Syph., Wien u. Leipzig, 1911, cx, 249.

[20] California State Med. Jour., Sacramento, 1911, ix, 255.

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[21] Laryngoscope, St. Louis, 1911, xxi, 201, 671.

[22] St. Petersb. med. Wchnschr., 1911, xxxvi, 359.

[23] Bull. et mém. Soc. méd. d. hôp. de Paris, 1911, Series 3, xxxii, 567.

[24] Ueber die Pathogenese der Salvarsantodesfalle, 1913, Urban and Schwarzenberg, Berlin, Wien.

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[25] Monatsh. f. prakt. Dermat. Hamberg u. Leipzig, 1911, liii, 591.

[26] Ann. de Dermat. et Syph., Paris, 1913, 5 s., iv, 98.

With due regard to the usual contra-indications, Klokow[31] tried the effect of salvarsan (0.2 to 0.6) upon twelve tuberculous sanatorium patients with visible luetic manifestations and positive Wassermann reactions. Only one dose of salvarsan (0.4) was given to the first six, classified as in the first stage and without tubercle bacilli, and all did well. They were from twenty-two to thirty-seven years of age. One was a patient with beginning secondaries; another, denying a luetic infection, showed a positive Wassermann; and in the remaining four, syphilis had been contracted from three to eleven years previously. Two showed a subsequent but very insignificant general reaction, and one a very slight and transitory rise of temperature. None exhibited any focal reaction. To the second 6, in the second and third stages of pulmonary tuberculosis, he gave one or more doses according to their condition. During the treatment two lost their bacilli and have remained without bacilli since; and the pulmonary lesions of three of them showed improvement. In none of the 12 could he detect any ill effects which could be attributed to the salvarsan treatment. All who were in a sufficiently good social condition to obtain proper care improved generally. A summary of the latter 6 cases follows: Case VII, aged thirty-eight years, pains in chest, apathy, anorexia, for six years frequently unable to do his work, symptoms intensified for eleven months, plus cough, expectoration, fever, profuse night sweats, weakness, loss of weight; right upper, fairly extensive process with rales, right lower, pleural rub and emphysema, left, slight, inactive lesion; Wassermann, von Pirquet, and tubercle bacilli positive, marked red scleræ: when apyretic, salvarsan (0.25), no discomfort, no fever, but a transitory focal reaction in lungs and scleræ; eighteen days later, salvarsan (0.3), in six hours fever, followed by general and focal reaction, then prompt improvement; two months later, both general and local improvement, tubercle bacilli absent. Case VIII, aged thirty-five years, a questionable luetic infection, ten years before, untreated; for six months, loss of weight, increasing expectoration, recently sweats; right apex inactive lesion, left less extensive but active and with rales; numerous mucous patches; Wassermann, von Pirquet, tubercle bacilli, all positive: salvarsan (0.5), in six hours slight pulmonary focal reaction, increasing expectoration and very slight fever, followed by prompt general and local improvement, one month later acute bronchitis, but improvement persisted, and weight increased. Case IX, aged twenty-nine years, lues for eight years, four inunction cures; double apical catarrh; Wassermann and von Pirquet positive, tubercle bacilli negative; salvarsan (0.6) without reaction, increase in weight. Case X, aged thirty years, lues three years previously, four inunction cures; cough for three years, change of climate with benefit, for two months worse, cough increasing, expectoration frequently bloody, loss of strength, sweats; right apex active process with rales, left inactive, left cervical glands below jaw enlarged; Wassermann, von Pirquet, positive, bacilli in sputum: salvarsan (0.6), in six hours, slight focal reaction, and slight increase in expectoration, five days later, glands still more enlarged, fever, latter disappeared after extraction of teeth; eleven days later: salvarsan repeated, slight transitory hemoptysis and fever; twenty-four days after salvarsan, sudden marked enlargement of glands, fever, dyspnea, operation, no reaction (glands not examined microscopically): salvarsan (0.3) twice in one month, very slight focal reaction, marked improvement, tubercle bacilli and rales disappeared. Case XI, aged thirty-two years, fourteen years before, a questionable luetic infection untreated for past year, cough, gradually increasing expectoration, sweats, loss of strength, last few weeks hoarseness; right, active lesion with rales; left, inactive; left vocal cord inflamed and covered with secretion; Wassermann, von Pirquet, tubercle bacilli, all positive: tuberculin emulsion, general improvement, but lungs did not clear up and rales appeared at left apex: salvarsan (0.6), followed by a marked pulmonary focal reaction and slight transient fever, and then lungs became drier; three weeks later: salvarsan (0.4) followed by same reaction; three weeks later, decided diminution of rales, marked improvement in vocal cord, discharged with few bacilli in sputum, weight much increased. Case XII, aged twenty-eight years, eight years before, a suspicious primary sore but no treatment; for two years, cough, bloody expectoration, sweats; improved at hospital, relapse with loss of strength, chest pain, cough, expectoration, sweats; double apical lesion, rather extensive. right with rales; Wassermann, von Pirquet, tubercle bacilli, all positive; gradual increase and extension of the process and lighting up of activity at left: salvarsan (0.3), six hours later, transitory, pronounced; focal but no general reaction nor fever, weight increased, general but no local improvement till four months later.

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[27] New York Med. Jour., 1913, xcvii, 551.

[28] Month. Cycl. and Med. Bull., Philadelphia, 1913, vi, 333.

[29] Lyon méd., 1913, cxxi, 97. Bull. Soc. méd. des hôp. de Lyon, 1913, xii, 466, 536.

[30] Clinique, Paris, 1913, viii, 338. Riv. internaz. di clin. e terap., Napoli, 1914, ix, 69.

[31] Berl. klin. Wchnschr., 1913, l, 1754.

These excellent results were, to be sure, obtained in patients under careful observation and under sanatorium treatment. The lapse of time intervening between the treatment administered and the writing of the report is, of course, relatively short for a critical judgment upon patients with so chronic a disease as tuberculosis.

Jeanselme, Vernes, and Bloch,[32] influenced by the frequently unfavorable effect of mercury upon patients with tuberculosis, by the well-known utility of any form of arsenic against tuberculosis, by the stimulating action of salvarsan upon the blood-making organs and upon general nutrition, and not intimidated by the possibility of awakening a dangerous congestive reaction in pulmonary lesions by the intense vasomotor effect of the new drug, followed for three years the effect of salvarsan or neosalvarsan upon 13 patients with combined syphilis and tuberculosis. In 5 advanced cases no benefit was noted upon either the general or the local condition; but no aggravation was produced. From the authors' description it is very questionable whether or no the treatment employed produced "no aggravation," just as it is difficult to understand why they chose three such cases as I, III and V without any evidence of active lues except a positive Wassermann in the last mentioned, and yet all so manifestly clinical problems in advanced stages of tuberculosis. The doses employed in Case I were too large and certainly in Case V the interval too brief. Although active syphilis co-existed in Cases II and IV, here too smaller doses and longer intervals would have been more appropriate in such serious and advanced tuberculous disease. The luetic infection was manifestly active, and the more striking clinical factor in the two cases next cited, with cavities or softening; but the beneficial effect of the drug, though apparent, was only transitory. The doses selected were more appropriate but could well have been smaller, and the interval in Case VII was too brief. Their most encouraging results were noted in the 6 following cases: Case VIII, aged thirty-five years, ulcerating syphilide, infection three years previous, Wassermann positive; both apices, scattered consolidation, recently a profuse hemoptysis, two series of "hectine" (0.1), poorly tolerated, but syphilitic lesions cicatrized, Wassermann still positive: salvarsan 0.5, 0.12, 0.2 four times from September 2 to December 6, 1911; no ill effect, increasing weight, general improvement: 0.25 repeated five times from December 9 to January 6, 1912: 0.25 followed by 0.3 four times from February 14 to March 19, 1912: discharged in April, condition excellent, no further hemoptysis, gradual fall of temperature, from between 37.2° and 38.8° before treatment to 37° after first course, where it remained except for one brief rise. Case IX, aged twenty-three years, recurrent roseola, pale, puffy, weak, anemic, dyspneic; rough blowing expiration, at both apices: neosalvarsan (0.15), followed by 0.3 seven times from August 30 to October 7, 1913; increased weight, improved color, rapid general improvement: neosalvarsan 0.3, 0.6, and 0.75 four times, general condition excellent on February 20, 1914. Case X, aged 31 years, February, 1913, secondary syphilis; for past two months, cough, expectoration, fever, sweats, loss of weight; both apices slightly dull, right rough cog-wheel inspiration and crackling rales: salvarsan, 0.15 three doses, 0.2 and 0.25 twice from February 18 to March 25, 1913, fever and sweats ceased, general improvement. Case XI, aged forty-five years, September, 1912, roseola, Wassermann positive, tuberculosis for six years; at entrance nauseating cough, bloody sputum, night sweats, emaciated, dysenteric enteritis; right apex, slight dulness, rough breathing and crackling rales; previously received fifteen injections of biniodide, followed by paroxysms of suffocation, nauseating cough and bloody sputum: salvarsan, 0.3, 0.35, 0.4, four times from October 15 to November 19, 1912, vomiting subsequent to first doses, otherwise steady improvement; March 3, 1913, cough and active signs in chest disappeared, Wassermann negative; July 2, general condition excellent, gain in weight, rough respiration at left apex; February 16, 1914, general condition good, slight dulness and few subcrepitant rales at left apex. Case XII, aged twenty-eight years, epididymitis, extensive perforation of palate, destruction of pillars and uvula, weakness, extreme pallor, night sweats, marked emaciation; right apex, rough blowing respiration: salvarsan, 0.3 twice, 0.4 four times from October 8 to November 12, 1912; after third dose rapid improvement, gain in weight, cicatrization of palate, pulmonary signs without change. Case XIII, aged fifty-two years, buccal leucoplakia, typically fissured tongue, positive Wassermann, cough, hemoptysis, emaciation, anemia, fever, night sweats; dulness at both apices especially right, rough breathing, moist rales, nummular sputum loaded with tubercle bacilli; two days previously, two very profuse hemoptyses: salvarsan, 0.3 six times during December, 1911, and January, 1912; no further hemoptysis, fewer rales, fever and cough disappearing, better color, weight increasing, rapid general improvement, resumed work; December, 1912, left pleurisy, sick three months; October, 1913, loss of weight, fatigue, pallor, bacilli in sputum; apices, rough interrupted breathing but no rales; marked enlargement of tail of left epididymis and induration of vesiculæ, abundant mucopurulent uretheral discharge, appearing suddenly but painless: salvarsan 0.15, 0.2, 0.25, neosalvarsan 0.45, 0.65, 0.6 twice during December, 1913, and January, 1914; general improvement, increase of weight and color, no pulmonary setback.

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[32] Bull. et mém. Soc. méd. d. hôp. de Paris, Series 3, 1914, xxxvii, 340.

The doses employed in these six cases, all very much less acute and advanced than in the first two groups, were more appropriate; certainly the results were more striking. Following the discussion of their report, Renon illustrated the harmlessness of and the excellent toleration to the drug in two similar patients, to whom he administered 0.15 and 0.2, and in four patients with uncomplicated tuberculosis who tolerated perfectly 0.1 to 0.15; but, in the latter, no specific action of the drug upon the tuberculous process could be detected. Belin tried salvarsan upon several patients with definite tuberculosis and recent secondary lues; both diseases always improved and in two instances were at least temporarily cured.

At Laennec Hospital, Bernard and Paraf[33] treated with salvarsan 9 patients with evidence both of tuberculosis and of syphilis. Of the 3 recently infected with the latter disease, 2 (Cases II and IV) had an active pulmonary process, the first dose of neosalvarsan was followed by a Herxheimer reaction, and in all three the antiluetic effect of the drug was rapid and excellent. A brief summary of their cases follows: Case I, aged twenty-six years, primary five years before, Wassermann positive, recent acute tuberculosis with softening and cavity formation, hemoptysis and anemia: successful artificial pneumothorax several times, later complete collapse; followed by seven doses of neosalvarsan (0.5 to 0.7) in three months; excellent result. Case II, aged twenty-eight years, early secondaries breaking out during a recent exacerbation of chronic phthisis with softening, cavity formation and bacilli: five doses of neosalvarsan (0.3 to 0.75) in five weeks; rapid improvement after third dose. Case III, aged thirty-nine years, cerebrospinal lues (tabetic) with positive blood and spinal fluid, fibroid phthisis, without demonstrated bacilli: seven doses of neosalvarsan in nine weeks (0.37 to 0.7); general improvement. Case IV, aged seventeen years, diffuse secondaries during tuberculous activity at one apex: four doses of neosalvarsan in three weeks; rapid disappearance of evidences of syphilis. Case V, aged forty-five years, lues twenty-two years before but without symptoms at time of observation, Wassermann positive; chronic tuberculous polyadenitis with suppuration: three doses of neosalvarsan without focal glandular reaction or any other recognizable effect. Case VI, aged forty-eight years, lues twenty-five years before with recent cerebrospinal involvement; advanced caseous pulmonary, renal, and bladder tuberculosis; seven doses of neosalvarsan (0.25 to 0.3); curative result upon syphilitic symptoms. Case VII, aged fifty-eight years, lues thirty years before, Wassermann positive; tuberculous ulcer of skin and fibroid phthisis: three doses of neosalvarsan (0.2 to 0.45) well borne. Case VIII, lues twenty-two years before, Wassermann positive; active fibroid phthisis: three doses of neosalvarsan (0.3 to 0.6) in three weeks, well borne three and a half weeks later; Wassermann negative. Case IX, aged thirty years, lues recent, profuse hemoptysis following prolonged course of mercury, six months later, pleurisy following more mercury: series of neosalvarsan well borne.

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[33] Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, 3 s, xxxvii, 357.

They conclude that the existence of pulmonary tuberculosis offers no special drawback to the proper administration of salvarsan; believe in the selection of moderate or small doses especially in cachectic cases with advanced lesions; emphasize the excellent results obtained upon the syphilitic manifestations and upon the general condition, as well as the perfect tolerance of patients with chronic tuberculous lesions even when advanced, progressing or combined with cachexia; but they failed to note any beneficial effect upon the actual tuberculosis. They did not employ the drug in acute tuberculosis. Sergent's experience mentioned in the discussion of their report confirmed all their conclusions.

Blinder[34] cites the case of an alcoholic with a positive Wassermann, a history of gonorrhea at sixteen years, of influenza and a fistula in ano two years before, and with a sudden onset of pulmonary symptoms and signs but without bacilli in sputum. Mercury and iodide of potash were followed by pronounced general and pulmonary benefit; salvarsan (0.6) expedited the cure. Hartley[35] tried neosalvarsan in 16 patients with tuberculosis at varied stages (only 1 of which was proved to be combined with lues) and in 14 obtained improvement. In nearly all of them its effect was especially striking in reducing the pyrexia which had resisted all the usual measures previously employed. He acknowledges that the rest and favorable surroundings may have been important factors. He cites 4 illustrative cases with temperature charts. The latter suggestively support his belief in the antipyretic and general beneficial effect of the drug. The proved luetic patient was a male, aged thirty-one years, with a severe cough dating back five months, emaciation, night sweats, afternoon temperature of from 99.2° to 101.6°; consolidation of both apices and of upper part of right lower and excavation of right apex; profuse expectoration with only a few bacilli after several fruitless searches; extreme hoarseness, a luetic laryngitis, and a markedly positive Wassermann; the fever persisted despite rest and the usual hygienic measures: neosalvarsan 0.9 followed only by malaise, in seven days temperature normal but rose again: neosalvarsan 0.9, salvarsan 0.4 (Joha, intramuscular), and neosalvarsan 0.9, discharged markedly improved in every way and with a negative Wassermann but without change in the pulmonary signs.

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[34] Med. Rec., New York, 1914, lxxxvi, 330.

[35] Lancet, London, 1914, i, 1602.

By far the largest group of cases has been recently reported by Fagiuoli[36] from M. Ascoli's Pathological Institute at Catania, and the treatment was so carefully and systematically carried out that a brief summary of the cases is included in this review. His material was collected during four years at the Ferrarotto Sanatorium, where he found lues in 60 to 65 per cent. of the male patients with tuberculosis. He usually selected neosalvarsan, began with 0.1, increased only 0.1 or at most 0.2 each time, and gave four or five consecutive doses. Most of his patients also received several intramuscular injections of calomel either some time before the administration of salvarsan or after the completion of one or more series of injections of the latter, and its effect was generally striking and very encouraging. The majority had the benefit of sanatorium and climatic treatment as well. Case I, aged twenty-three years, for one month, persistent cough with profuse mucopurulent expectoration, pains in right chest, constant headache, anorexia, insomnia, general weakness, temperature 37.5° to 38°, lost 6 kilos.; left apex rough breathing, right, few dry rales; right subspinous and base rales, no bacilli, von Pirquet negative: general treatment; ten days later, roseola, hoarseness, mucous patches, Wassermann positive, confessed infection two or three months before: neosalvarsan 0.1, 0.2, 0.3, 0.5, then calomel 0.1 three times; complete cure, Wassermann negative; two years later, condition excellent. Case II, aged twenty-four years, lues one year previously: calomel three injections, prompt cure; one month later, increasing cough and sputum, intense headache, gastro-intestinal disturbance, slightly dysphagic, general weakness, loss of weight, occasional fever, no bacilli; no benefit from general treatment; sputum became pinkish; diffuse rales mostly at right base and right mid lobe; general adenitis, pharyngitis, mucous plaques; Wassermann positive, von Pirquet negative: calomel 0.5 six times, neosalvarsan 0.2, 0.3, excellent result. Case III, aged twenty-nine years, lues at twenty-four, cured with calomel; one and one-half years later, morning cough, dry, then with mucopurulent expectoration, no bacilli, hoarseness, anorexia, weakness, anemia, no fever: general and climatic treatment; six months later, much better except cough; one year later, return of above symptoms with fever, increasing laryngeal catarrh, no bacilli, von Pirquet negative, but diagnosed as pulmonary tuberculosis; rough inspiration and few rales right apex anteriorly, and at left and right apices posteriorly, still more rales at left base: climatic treatment till April, 1913; one and one-half years later, increased cough and persistent sputum, 125 to 150 grams daily, laryngitis, fever, general symptoms and chest pains, chest signs same, no bacilli, rash, confessed lues, Wassermann positive: calomel plus neosalvarsan 0.1, 0.2, 0.3, 0.5, marked improvement first on rash, larynx, general condition, cough, expectoration; increasing weight, finally only slight morning cough and few rales left.

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[36] Ann. di Clin. Med., Palermo, 1915, vi, 23.

In the next six cases, plainly predisposed to tuberculosis, the luetic infection evidently activated a latent pulmonary focus, which, except in Case X, broke out within two years of the onset of the specific disease. Although prompt and vigorous antisyphilitic treatment is usually a distinct help to combat such an awakening of tuberculosis, some of these patients obtained little, and others, no apparent benefit.

Case IV, aged twenty-six years; mother died of phthisis; at sixteen years, bronchial catarrh cured in a few months; lues, 1912, no treatment, no signs; in May, dry cough, then with mucopurulent sputum, anorexia, weakness, emaciation, sweats, fever, headache, bacilli; in July at sanatorium, bronchopneumonia of right upper and middle lobes, rales left apex, Wassermann positive: neosalvarsan 0.1, 0.3, 0.4, 0.5; good general and pulmonary effect but Wassermann still positive; January, 1913, pulmonary signs unchanged, increasing general symptoms, mucous patches: neosalvarsan 0.4, 0.5; calomel 0.5 four times; improvement decided, Wassermann negative, condition remained excellent. Case V, aged twenty-one years: father luetic, died of phthisis; numerous attacks of bronchial catarrh, alcoholic; lues March, 1910, in three months secondaries: few injections mercury iodide; one year later, cough, mucopurulent sputum, anorexia, weakness, emaciation, anemia, slight fever, severe hemoptysis, bacilli; sanatorium, October, 1911; diffuse bronchopneumonia with cavity formation entire right chest, Wassermann positive: neosalvarsan 0.35: calomel 0.1, four times; slight general improvement, no pulmonary change; artificial pneumothorax, with excellent effect and left sanatorium March, 1913; calomel six times, very little cough, no signs of lues, remained well. Case VI, aged twenty-six years; mother died of phthisis; patient in excellent health, robust, tubercle bacilli in blood (?); February, 1912, without symptoms or signs, von Pirquet slightly positive; one year later lues: mercury iodide, twenty times; four months later, exudative pleurisy left chest, very severe and prolonged, fever high, chest tapped twice, bacilli in serum, increasing cough with sputum but without bacilli and no signs of pulmonary consolidation; left hospital, but weakness, anorexia, and cough persisted, fever recurred, sputum pinkish, bacilli; rales at right apex and base, pulmonary process extensive and diffuse, nutrition very poor, Wassermann positive: neosalvarsan 0.1 to 0.5, five times; slight benefit in general condition, transitory tendency to arrest; following hemoptysis, an extension of process. Case VII, aged thirty years; in childhood, cervical adenitis and operation; at nineteen years, bronchial catarrh for several months, cured; March, 1912, sanatorium, lues five months before; two months later, severe rapid phthisis; diffuse bronchopneumonia left, slight process with rales right apex, bacilli; Wassermann positive, enlarged glands, roseola: neosalvarsan 0.1 to 0.5, five times, with excellent result both pulmonary and general; Wassermann negative; September, 1912, left sanatorium, went to the country and worked; signs very slight; one year later, calomel eight times, recently Wassermann negative, excellent condition except for few rales; no signs of syphilis. Case VIII, aged twenty years; father died of phthisis; at twelve years exudative pleurisy, cured in two months; at eighteen, lues; two months later, secondaries: mercury iodide thirty times; cured except for chronic laryngitis; two years later, cough, mucopurulent sputum, chest pains, sweats, increasing weakness, emaciation, laryngitis worse, dysphagia, aphonia, dyspnea; sanatorium; three months later, in wretched condition; rales and rough breathing at right apex, bacilli; Wassermann positive: neosalvarsan 0.1 to 0.5, five times, larynx benefited first, ulcers cicatrized, increasing weight and general improvement; one year later: calomel 0.5 four times and mercury iodide thirty times; left sanitorium, Wassermann negative, no bacilli, only slight cough and few rales. Case IX, aged thirty years; mother and brother died of phthisis; in youth, for several months, bronchial catarrh; at sixteen, prolonged typhoid with pulmonary symptoms; at twenty-five, pleuropneumonia, two months in hospital; November, 1911, lues; three months later, secondaries, increasing cough, mucopurulent sputum, diffuse chest pains, weakness, anorexia, emaciation, sweats: calomel three times, and few inunctions of mercury; syphilis cured, general condition improved but cough increased with mucopurulent occasionally pinkish sputum; still worked; January, 1912, sudden hemoptysis, bacilli; in March, sanatorium; diffuse bronchopneumonia, consolidation with cavity, at left, rales at right apex; Wassermann positive, mucous patches: neosalvarsan 0.1 to 0.6, five times; lues cured, pulmonary signs arrested; general condition improved: tuberculin; March, 1913, signs much improved, left sanatorium, did not follow advice, returned in a few months and died. Case X, aged thirty-eight years; father died of phthisis; at twenty-one left exudative pleurisy, three months in hospital; at twenty-seven, lues: calomel eight times and several inunctions of mercury; cough, mucopurulent sputum; both disappeared in a few months; at thirty-five years, February, 1912, gumma in nose, ulceration and necrosis of bone; bronchopneumonia; two months in bed: neosalvarsan once, nose began to improve, also pulmonary process; left hospital with cough, chest pains, mucopurulent sputum, occasional slight fever; later, general weakness; returned for few months; bacilli; diffuse bronchopneumonia at left, rales at right apex; Wassermann negative, luetin positive: neosalvarsan, increasing doses five times; calomel, 0.5, three times, marked general improvement but no change in lungs.

When lues is acquired by patients in poor general condition with severe and diffuse pulmonary tuberculosis, and with other organs affected, nearly all of them do badly. Under such conditions antiluetic treatment, even if active and prompt, will be of little or no benefit, as is well illustrated by two of the next three cases:

Case XI, aged twenty-nine years. February, 1910, severe hemoptysis, followed by pulmonary symptoms; sanatorium, August, 1911, condition grave, fever; in both chests diffuse bronchopneumonia, cavity formation right; four months' treatment at sanatorium with diminishing fever, but no change in pulmonary signs; worked one year in this condition; January, 1913, lues and secondaries: calomel, 0.2, four times, improved the luetic symptoms but general condition, already serious, became much worse; sanatorium in April in very bad condition, with fever and cough; Wassermann negative: neosalvarsan 0.1, 0.3, 0.4, without effect, died. Case XII, aged thirty-five years, cough, mucopurulent sputum, chest pains, sweats, anorexia, weakness, wretched nutrition, and grave general condition for two years; diffuse bronchopneumonia, rales at right apex, rough breathing left; sanatorium, March to July, 1912, without improvement; lues in December: neosalvarsan, given once intramuscularly; calomel 0.5, three times; three months later, marked aggravation in cough, sputum, dyspnea, and fever; sanatorium, April, 1913, both sides now diffuse pulmonary process with cavity formation right; Wassermann positive: neosalvarsan, three times, brief general improvement, then severe hemoptysis, rapid aggravation, died. Case XIII, aged twenty-five years, 1909, phthisis, slowly advanced; sanatorium

April, 1911; fever, diffuse bronchopneumonia at left, slight process with rales right apex, adhesions prevented artificial pneumothorax; general condition improved, no change in pulmonary condition, resumed work in September; lues in December; one month later, afternoon fever, increasing cough and expectoration; sanatorium, February, 1913, chest same; Wassermann positive: neosalvarsan, 0.1 to 0.5, five times, general as well as a gradual improvement in pulmonary condition; May, 1913, tuberculin; February, 1914: neosalvarsan three times; now in excellent condition, no signs of syphilis, Wassermann negative, chest signs much improved.

The luetic infection in Cases XI and XII aggravated both local and general condition and contributed to the fatal issue. The relatively good condition of Case XIII, at the onset of lues, favored the treatment and therefore improvement eventually resulted.

When a tuberculous lesion is of limited extent, well localized and advancing slowly, the acquisition of lues would seem almost to render the bacillary disease less serious, at least after subsidence of the initial acute symptoms. Antiluetic treatment assists; but the final result depends upon the tuberculous process itself and its appropriate treatment:

Case XIV, aged twenty-nine years; mother died of phthisis; 1907, cough, sputum, pains in chest, anorexia, weakness, fever, bacilli: to country; one year later, general improvement, only occasional cough and slight sputum, bacilli few; diffuse but slight pulmonary signs; worked three years, in good general condition, same few signs in chest; February, 1911, lues: mercury iodide; syphilis improved, but general condition became aggravated, cough increased, sputum, fever, weakness, emaciation; September, severe hemoptysis; October, sanatorium; diffuse bronchopneumonia right chest, rales left apex; Wassermann positive: neosalvarsan, five times, with gradual improvement; chest signs much diminished, Wassermann slightly positive; April, 1913, discharged; in winter: calomel 0.5, eight times; signs very slight, bacilli very rare, Wassermann negative. Case XV, aged twenty-eight years, hemoptysis at fifteen; February, 1911, sanatorium, slight fever; bronchopneumonia upper and mid right, apical catarrh left; in winter, cough, sputum, slight fever, general improvement, signs unchanged, worked about one year, condition remained same; January, 1913; lues, much worse, increasing cough, slight dyspnea, anemia, weakness, emaciation, fever: calomel 0.5, seven times, better, chest same, Wassermann positive; August, secondaries, respiratory symptoms increased, profuse hemoptysis, very severe anemia and poor general condition; diffuse bronchopneumonia entire right chest, slight activity left apex, Wassermann positive: neosalvarsan, increasing doses, four times, general improvement, but fever and signs persisted; December, neosalvarsan, 0.3 twice, 0.5, with prompt decided improvement; tuberculin, condition continued to improve, Wassermann negative, signs less diffuse and less marked. Case XVI, aged thirty-five years, phthisis at twenty years, slight hemoptysis, four or five times; in hospital few months, condition very grave, then worked with only slight cough and sputum; at twenty-six, lues with secondaries and exacerbation of other symptoms: calomel and mercury inunctions; pulmonary condition worse; readmitted: general treatment, improvement resulted, worked with only cough; November, 1912, gumma, general condition much worse, cough, sputum, fever, bacilli, Wassermann positive: salvarsan 0.5; calomel 0.5, four times, with considerable improvement, except pulmonary signs, then artificial pneumothorax with excellent result, Wassermann negative. Case XVII, aged twenty-nine years, summer of 1911, slight hemoptysis, alcoholic, bad hygiene but general condition same till September, 1911, when received a blow in right chest with pain, respiratory disturbance, fever; bronchopneumonia in right upper chest, exudative pleurisy left: tapped, improved, worked; March, 1912, lues, no treatment, respiratory disturbance increased after few months; sanatorium, grave condition; diffuse consolidation entire left chest, slight activity at right apex; Wassermann positive, hemoptysis: neosalvarsan, 0.1 to 0.5, five times, improvement but not rapid; October, rash, mucous patches, headache: neosalvarsan twice; calomel 0.5, four times, slow improvement in luetic also in pulmonary symptoms; left sanatorium, Wassermann positive, signs less, poor hygiene but worked one year with little change in condition; winter 1913–1914, exacerbation and death following acute alcoholism.

The next case illustrates the sclerotic effect which, after the preliminary activity has ceased, follows the luetic infection and is actually beneficial as has been so frequently emphasized by E. Sergent.[37]

Case XVIII, aged twenty-six years, double pneumonia at fourteen years, alcoholic and bad hygiene but well and strong till nineteen; 1907 phthisis, winter cough, mucopurulent sputum, bacilli, weakness, anorexia, frequent sweats: general treatment without improvement; September, 1911, general condition and nutrition fair; diffuse bronchopneumonia right chest, slight activity left apex; October, 1912, lues with early secondaries: calomel 0.4, three times, mercury cyanide, ten times; accentuation of pulmonary symptoms with slight fever and subsequent hemoptysis: to country, remained in bed and improved; March, 1914, signs much less, few rales right, excellent general condition, Wassermann positive: neosalvarsan, 0.1 to 0.5, five times, marked improvement bacilli very rare, still further dryness at apices. The author, however, attributes the benefit obtained by this patient, largely to climatic and general measures.

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[37] Syphilis et Tuberculose, Paris, 1907.

The next case illustrates how virulent the luetic virus may be: Case XIX, aged twenty-two years, left exudative pleurisy with good recovery, except for cough, later with sputum; February, 1912, rales at right apex, bacilli very rare; toward end of 1912, lues, increasing respiratory symptoms, fever, became worse: calomel, 0.5, seven times; syphilitic symptoms cured, general condition poor; five weeks later, general eruption: salvarsan 0.5, rash disappeared; but tuberculous lesions spread and patient died in two months.

The remaining 4 cases illustrate the grafting of a tuberculous infection upon tertiary luetic lesions of the larynx or lung, and confirm Sergent's claim that the election of this sclerotic soil favors a chronic course or cure of the secondary invader. Antiluetic treatment exerted a favorable influence upon all; but, coinciding with the outbreak of gummata, XXI and XXII showed a temporary aggravation, both local and general:

Case XX, aged thirty-eight years, lues at seventeen years; mercury iodide, forty times in two successive years, no symptoms except laryngitis; six years later, cough, sputum, sweats, slight fever, bacilli in sputum, but worked in good general condition; sanatorium in winter of 1910; bronchopneumonia right upper and middle, slight at left apex; one year later, left sanatorium much improved; three months later, increasing laryngitis with fever; returned April, 1911, with same signs, aphonia, dysphagia, dyspnea, ulcerative laryngitis; Wassermann positive: local treatment without benefit: neosalvarsan, 0.1 to 0.5, five times; in four months, laryngitis gradually cured, symptoms in lungs improved: tuberculin; February, 1913: neosalvarsan, 0.2 to 0.4, three times; left sanatorium March, 1913, cured, without sputum, very marked improvement in signs, Wassermann negative; continued well. Case XXI, aged forty-four years, lues at nineteen years: treated with mercury, no symptoms, except child died in early infancy, until at thirty-two years, gumma: calomel four times; at thirty-six, cough, slight bloody sputum, bacilli very few, worked; at forty, laryngeal catarrh and gumma, respiratory symptoms increased, slight hemoptysis, failure in general condition; sanatorium 1912; bronchopneumonia diffuse right, inactive left apex, bacilli positive, Wassermann positive: neosalvarsan, 0.1 to 0.5, five times, improvement prompt in luetic symptoms, gradual in pulmonary and general condition; discharged; April, 1913, signs less, bacilli few, Wassermann negative; continued improvement. Case XXII, aged fifty years, lues at twenty-two, secondaries late: few mercury injections and inunctions, cured; alcoholic, poor hygiene yet well till forty when had several hemoptyses with fever, temperature normal in one month, but cough, mucopurulent occasional bloody sputum, anorexia, weakness persisted; hospital, bacilli, in two months improved, worked, only cough remained;

at forty-six, exudative pleurisy, increase in fever, tapped, condition serious; consolidation at both apices; general improvement for two years with only an occasional hemoptysis; November, 1912, diffuse pulmonary lesion, increasing cough, sputum, pain in chest, headache, fever, gumma, Wassermann negative, luetin positive: neosalvarsan, 0.1 to 0.6, six times; lues cured, signs and pulmonary symptoms improved; and retained improvement except cough and very slight hemoptysis. Case XXIII, aged thirty-six years, lues at twenty, without treatment or symptoms except slight hoarseness for two years; at twenty-eight, exudative pleurisy right, cured in one and one-half months; at thirty-three (1911), symptoms of phthisis, cough, mucopurulent sputum, bacilli, sweats, fever, hemoptysis twice; April, 1912, sanatorium, condition very serious, Wassermann positive; bronchopneumonia right middle and lower, apical catarrh left; two months later ulcer of larynx: local treatment without effect: neosalvarsan, 0.1 to 0.5, six times, marked improvement of larynx but none in other symptoms, left sanatorium one year later with fever and a very diffuse process; four months later died from hemoptysis. Case XXIV, aged forty-eight years, lues at twenty-five years, only slight treatment; at thirty-three years, gumma on forehead, disappeared without treatment; at thirty-nine years cough, sputum, pains in chest, fever, increasing weakness, emaciation, slight hemoptysis; hospital six months, bacilli, improved but sputum bloody; worked till February, 1912, then suffered a blow and had hemoptysis, anemia, increasing respiratory symptoms; sanatorium in July, in fair condition and nutrition; diffuse bronchopneumonia left, consolidation right lower; very slight headache, Wassermann negative, luetin positive: neosalvarsan, 0.1 to 0.5, five times, prompt improvement of specific, gradual of general symptoms, signs lessening in extent and degree.

Despite the serious general condition, and despite the very diffuse character of the pulmonary tuberculous lesions in many of the cases cited above, the author only once observed an intolerance to the drug; but neither a focal (tuberculin-like) reaction nor any phenomena of congestion. He also employed calomel freely and with no ill effect except upon two patients with intestinal disturbances and one with hemoptysis; he never employs iodide of potash because of the danger of reaction and congestion. Neither salvarsan nor neosalvarsan produced any improvement in a small series of strictly tuberculous patients (5 in the first, 2 in the second, and 2 in the third stages of pulmonary tuberculosis); and he further states that there is no evidence available which would lead one to expect any benefit from these arsenic derivatives unless syphilis co-exists. If antiluetic treatment be instituted in the early period of syphilization where a tuberculous infection already exists, a prompt recovery from the sudden insult occurs; and the individual regains or increases his powers of defense in the struggle against the tuberculous germ which he also harbors. If, on the contrary, tuberculosis develops in an old syphilitic, antiluetic treatment will always benefit the syphilitic soil, upon which and on account of which the tuberculous process develops.

He further concludes as follows: (1) The association of lues and tuberculosis is much more frequent than usually credited; (2) lues offers a striking predisposition for tuberculosis; (3) their co-existence is not necessarily fatal and many cases recover; (4) the development of tuberculosis in primary lues is generally due to reawakening of a latent tuberculosis and is apt to run a severe course; (5) tuberculosis developing in old luetics runs a benign course and tends to sclerose; (6) lues, developing in active pulmonary tuberculosis, always aggravates the general and the local condition; although if the tuberculous process is limited and torpid this aggravation is apt to be transitory; but if the pulmonary lesions are diffuse and serious, a fatal result will inevitably follow; (7) every case demands vigorous antiluetic treatment; it is always well tolerated and frequently produces a favorable effect upon the tuberculous process.

Culver[38] has recently described the striking effect of one dose of neosalvarsan (0.45) followed by mixed treatment upon a case of probable pulmonary syphilis which closely simulated tuberculosis, although two examinations of sputum were negative. The signs and symptoms of tuberculosis were promptly cleared up by treatment. Pontano[39] reviews his experience with 500 injections of salvarsan and neosalvarsan in various types of lues and in a few non-luetic conditions. He treated, with 23 injections, eight patients with pulmonary syphilis, six of whom entered the hospital for hemoptysis and in only one of whom it persisted. He merely states without any details that the treatment produced a general improvement, with diminished headache and fever; but did not alter the amount of expectoration, the physical signs nor the amount of aereation of lung as judged by the radiograms. Fischer[40] recently reported several deaths following the use of salvarsan; and of these two were patients with tuberculosis. In one of them, besides an involvement of the lungs and ulcers in the intestines, the autopsy showed that both adrenals were caseated and nearly completely destroyed; so that although the color of the patient's skin evidently might have suggested Addison's disease and thus prevented the employment of the drug (two doses 0.4 and 0.5, seven days apart) death could have been but slightly hastened. To the other, a marked alcoholic, an initial dose of neosalvarsan (0.45) in addition to mercury was given on the day of entrance and both drugs were apparently well tolerated. Six days later, the neosalvarsan (0.6) was repeated and the patient left the hospital. Four days after, he was brought back unconscious and in convulsions; the next day he died. Autopsy showed that death was probably caused by an acute alcoholic pneumonia, but also that he had an active and extensive pulmonary tuberculosis. The treatment was evidently injudicious. Chauffard and Le Conte[41] have quite recently reported an eruption of erythema nodosum which coincided with the appearance of early secondaries in a patient with syphilis and inactive tuberculosis (intense von Pirquet, radiogram revealing considerably enlarged mediastinal glands and consolidation in the upper left lobe). A series of injections of cyanide of mercury (fifteen doses of 0.01) was promptly followed by a disappearance of the erythema and a general improvement. Four weeks later a course of novarsénobenzol de Billon (0.15, 0.30, 0.45, 0.60, three times) was given intravenously from July 28 to September 5. After the first dose (0.6) the nodular erythema reappeared and became much intensified; to fade and disappear again within four days. The same nodular eruption reappeared though less vividly after the third and fourth doses (0.6); but only persisted three and two days respectively. They consider that the first outbreak of erythema was of a tuberculous origin, awakened by the incidence of the syphilitic infection, and they liken the reappearance of the eruption, following the larger doses of arsénobenzol to a sort of focal reaction, similar to that of tuberculin. Among 4000 routine tests upon hospital patients, Walker and Haller[42] found only three of the 90 cases of outspoken pulmonary tuberculosis with a positive Wassermann reaction. All the cases of tuberculous meningitis gave negative tests both in blood and spinal fluid. The pulmonary signs and symptoms of one case rapidly cleared up under salvarsan, mercury and potassium iodide.

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[38] Jour. Am. Med. Assn., Chicago, 1915, lxiv, 335.

[39] Policlinico, Rome, 1915, Sez. Medica, xxii, 145, 227.

[40] Deutsch. med. Wchnschr., 1915, xli, 908.

Fordyce[43] states: "I have treated a number of syphilitic patients who had at the same time tuberculosis. I find that by giving them small doses not more than 0.2 or 0.25 gram, at intervals of from two to four weeks, that the salvarsan has apparently a tonic effect on the patient. Patients with tuberculosis who are given salvarsan in large doses at frequent intervals I have found to react badly to the drug."

CONCLUSIONS. 1. The prompt employment of salvarsan or neosalvarsan is indicated in latent, chronic and moderately active tuberculosis: (*a*) as soon as the nature of an added infection is diagnosed with reasonable probability to be syphilis; (*b*) whenever the history, signs, or symptoms strongly suggest a previous luetic infection, particularly if such a patient is not improving upon the usually successful hygienic and climatic treatment for tuberculosis;

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[41] Annales de Médecine, 1915, ii, 563.

[42] Jour. Am. Med. Assn., Chicago, 1916, lxvi, 489.

[43] Personal communication.

but (*c*) active tuberculosis, acute tuberculosis, and diffuse miliary tuberculosis are usually definite contra-indications to the use of these new arsenic preparations; although in both the first two mentioned groups there will be found many luetic patients upon whom a small dose of salvarsan may well be tried and, unless followed by untoward effects, cautiously repeated in gradually increasing doses.

2. When tuberculosis infects or becomes active in a patient with secondary, tertiary or even latent syphilis, the careful employment of one of these drugs is also indicated.

3. The more active the tuberculosis, the smaller should be the initial dose; the slower its increase, the less frequent the interval, and the greater care and watchfulness required.

4. Tuberculin-like focal reactions may follow their administration, should be carefully watched for and if present, the location, intensity and character will frequently guide in the selection of the next appropriate dose or interval.

CLINICAL INVESTIGATIONS ON INTESTINAL AUTO-INTOXICATION, ESPECIALLY AS REGARDS THE QUESTION OF SPECIFICITY OF TOXIN.[1]

By Thomas R. Brown, M.D.,
BALTIMORE, MD.

We wish to present very briefly a few observations on the specificity of toxin or bacteria in certain cases of so-called intestinal toxemia or bacteriemia, not in an attempt to draw any definite conclusions from these observations, but rather to chronicle certain rather striking findings in the hope of stimulating discussion on this subject of so much interest and yet of such almost universal misconception. These cases, although few in number, were studied rather intensively in the hospital, where each was under careful observation for a period of at least four weeks; they comprised 3 cases of chronic eczema and urticaria, 1 of pruritus, 2 of so-called bilious headache, and one of choroiditis. The 3 cases of chronic extensive eczema with urticaria gave almost identical histories, the salient points of which were as follows:

Case I.—Young man, aged twenty-six years. Negative past history, except a little eczema all his life; hay fever every summer; an absolutely normal digestion before the present illness, except a slight tendency to constipation; rather nervous; moderate user of alcohol and tobacco. Present illness began nine months before he was seen by us—eczema of the big toe, gradually spreading until it now involves the whole body; has had many treatments, but all unsuccessful. The salient points of the physical examination were a very extensive eczema, scaly or weeping, with also some definite urticaria, a normal blood count, except 12 per cent. of the eosinophiles and 46 per cent. of neutrophiles; test meal: free hydrochloric 10, total 15; stool cultures aërobic normal, anaërobic sterile; test meal on leaving hospital, normal (six weeks later).

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[1] Read at the meeting of the Association of American Physicians, May, 1916.

Case II.—Man, aged fifty-four years. Absolutely negative family and past history; onset of present illness five months before, beginning on thighs, and now involving entire body, associated with attacks of urticaria and angioneurotic edema. Physical examination showed a moderately enlarged liver, a diffuse papular squamous eczema, with some urticaria, a normal blood count, the eosinophiles being but 2.5 per cent.; stool examination negative both as regards bacterial, chemical, and microscopic findings; test meal: free hydrochloric acid 18, total 30.

Case III.—Woman, aged forty years. Absolutely negative past history except tendency to constipation, with slight gastric indigestion. The patient had had a diffuse eczema with urticaria for over a year without definite cause. The physical examination showed this condition and was otherwise negative, except that the test meal showed a complete absence of free hydrochloric acid; the stool and the blood were normal.

Tests of cutaneous sensitiveness to proteins were made in all 3 cases by the method employed by Blackfan—milk, egg-white, horse serum, meat juice, and barley protein being employed. The first 2 cases showed marked hypersensitiveness to all the proteins, except that there was no reaction to egg-white in the second case and very slight in the first. The third case showed no cutaneous reaction to any of the proteins. In the first 2 cases a meat-free diet with no cereals brought about a rapid improvement leading to a permanent cure; in the third case the effects of such a diet were *nil*. In the first case, after two weeks of complete freedom from skin lesions, the giving of one egg reproduced within twenty-four hours the original cutaneous picture; but after another two weeks of meat-free diet, egg-white was given again in teaspoonful doses daily, gradually increased, subsequently feeding other proteins in a similar way, so that now his tolerance has been so increased that he is able to take eggs, milk, and simple meats in moderate amount with no ill effects. He as well as the second patient has now been entirely well for nearly a year.

The case of pruritus was most interesting in many respects. The patient was a very nervous woman with a negative past history, except for several mild abdominal attacks suggestive of appendicitis, and also the history of chronic constipation. The physical examination showed marked cecal stasis, with slight tenderness on deep palpation, verified fluoroscopically as being due to a chronic appendicitis. The pruritus, which was general, followed directly upon an acute attack of indigestion, about eight months previous to her visit to us, which seemed to be referable to eating crabs and milk, and had continued ever since, although markedly aggravated by excitement and worry, and alleviated by the simple life. The gastric examination showed a true achylia, the stool cultures were negative, while her protein sensitization test showed a marked reaction with milk, but none with the other proteins employed. On a low protein diet, practically meat-free, with milk entirely eliminated, and the administration of hydrochloric acid and attention to the constipation, the pruritus gradually disappeared, and has now been absent for more than a year, while the study of her gastric contents shows a return of hydrochloric acid, though still distinctly subnormal.

The 2 cases of bilious headache had practically identical histories —chronic constipation associated with periodical attacks of severe headache associated with an increase in constipation, nausea, and vomiting, and always relieved by free purgation, especially by calomel and salts. Each showed a complete absence of hydrochloric acid in the gastric contents, no hypersensitiveness to the protein substances employed, each was markedly relieved by a diet from which animal protein food was practically eliminated, and in each an increase in the bowel sluggishness, a typical bilious headache, and, what was most interesting, a temporary but marked increase in the size of the liver could be brought about by giving meat for a short period of time.

The last case was perhaps the most interesting of all, for this was the only one of our series in which the bacteriological study of the stool gave pathological findings. This patient had recurring attacks of choroiditis, always preceded by digestive disturbances.

Case IV.—A young woman, aged twenty-seven years. Had typhoid fever at eighteen years, chronically constipated for about thirteen years, necessitating the constant use of purgatives, while the present illness was simply a continuation of her old history of constipation, although getting gradually worse with weakness, gastric and intestinal indigestion, pain in the stomach and in the lower abdomen shortly after eating, not related to the menstrual function, with, for the past four years, attacks of eye-ache and recently distinct impairment of vision. The physical examination showed a marked visceroptosis, with a maximum degree of cecal stasis, and fluoroscopic evidence of chronic appendicitis, a negative Wassermann reaction, a moderate anemia, practically normal gastric contents, the typical ophthalmoscopic picture of repeated attacks of choroiditis with old, black hemorrhagic deposits, while the stool examinations, of which twenty-six were made in conjunction with Dr. Sylvester, at the Woman's Hospital, showed when the stool was acid nothing especially characteristic except occasionally a very few anaërobes, while with an alkaline stool the predominating organism was a large diplococcus, anaërobic, Gram-negative, with quite a number of a large and a small Gram-negative anaërobic bacillus.

The striking features of this case were (1) the apparently definite connection between the acute intestinal disturbances and the "eye-aches" of the patient, ophthalmoscopically recognized as acute attacks of choroiditis; (2) the fact that with these attacks the stools were always alkaline, while bacteriologically there appeared as the predominant microbes three Gram-negative anaërobes which we were unable to definitely identify, notably a large diplococcus, these anaërobes usually being practically absent when the stool was acid, while the diplococcus was isolated in pure culture from the appendix at the time of an appendicostomy operation performed later; (3) the extreme difficulty in keeping the stool acid even with a meat-free carbohydrate-rich diet, and enormous doses of an acid-forming bacillus—the Bacillus bulgaricus; (4) the considerable improvement brought about by a low protein diet, which was markedly increased by an appendicostomy with colonic irrigation through the new opening; (5) our ability to prophesy the choroidal attacks from the alkalinity of the stool and its large content in certain anaërobic bacteria.

When we speak of toxic symptoms we are unquestionably treading on debatable ground, and yet certain of the symptoms met with in these cases are explicable only on this basis. What is the cause of these toxic symptoms? Is it a toxin normally present or in excess? Has the protective mechanism become insufficient possibly due to repeated mild anaphylactic reactions, or is there a tendency toward an overgrowth of certain bacteria, notably proteolytic anaërobes, and may immunity be brought about in time? Whether these toxins are derivatives of the amino-acids we cannot say, but it is striking what slight changes in molecular constitution are necessary to convert the normal bases into products of great toxicity, and it is certainly possible that this may be brought about by the proteolytic intestinal bacteria. The work of Eppinger and Guttman in isolating two ptomains from the stool, one producing urticaria, the other asthma, is extremely suggestive in this connection. Whether these toxic anaërobes are always present in minimal amount, or whether they originate from external sources, such as tainted meat or pyorrheal pockets, has not been determined. That the poisons, produced by these bacteria or due to other causes, cannot often be demonstrated is not so much a proof of their absence as of their extreme complexity, and of the minimal amounts in which they must be present in urine, blood, and stool. The mechanical and surgical conceptions of intestinal stasis are quite insufficient to explain the symptom-complex presented. Back of the mechanics of digestion lies a problem far more complicated, far more difficult to solve, the problem of congenital or acquired hypersensibility to certain stimuli, the question of the overproduction of certain toxic substances, their chemical nature, and their possible specificity, and various questions involving more definitely physical factors, notably absorption and osmosis.

In our series it is hard to escape the conclusion that in the intestine certain substances are produced which in some instances are possessed of specific action associated with a hypersensitiveness to certain proteins not in themselves toxic but possibly capable of producing a reaction because of an acquired hypersensibility, and that therapeutically a marked improvement in symptoms and even a complete cure may be brought about by the elimination of these substances from the dietary. It is also suggested by a study of these cases that by giving these foods in gradually increasing amounts a marked increase in resistance may be produced. That in certain cases at least the symptoms are better explained on the basis of a bacterial infection of intestinal origin rather than upon that of a toxemia, and that in various cutaneous lesions, testing the cutaneous sensibility by intradermal injection of various proteins is of real value in determining whether or not the condition may be due to certain toxic bases of intestinal origin derived from the decomposition of certain protein foods. These reactions are apparently specific in character, that is, are only found to be present when the toxins produced have a specific effect upon the skin, and therefore these tests of cutaneous hypersensiveness to various proteins probably cannot be used as criteria of other conditions best interpreted as protein intoxications with manifestations elsewhere than in the skin.

STOCK-BRAINEDNESS, THE CAUSATIVE FACTOR IN THE SO-CALLED "CROSSED APHASIAS."

By Foster Kennedy, M.D., F.R.S. (Edin.),

CONSULTING NEUROLOGIST TO BELLEVUE AND NEW YORK HOSPITALS; LATE MÉDECIN-CHEF, HÔPITAL MILITAIRE, RIS ORANGIS, FRANCE.

"La théorie de la gaucherie cérébrale, pleine d'obscurités, contredite par les faits, ne peut servir à expliquer pour les partisans du centre de Broca les destructions de ce centre sans aphasie."[1]

These words by Pierre Marie and his colleague Moutier, eight years ago, largely formed the basis of a momentous attack on the classical opinions concerning the positions of the centers governing the functions of speech. As a result of this first onslaught the iconoclasts won for their objections a wide hearing and many disciples, whose ardor has since been somewhat cooled as much by the lapse of time as by the mobilization of the forces of the classicists. Nevertheless, as a result of these dialectics, the whole subject of the causation of the aphasias has been shaken, and not a few of us have failed to decide for ourselves as to the validity of the evidences adduced on both sides.

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[1] L'Aphasie de Broca., Moutier, 1908, p. 127.

The cause of this indecision lies in the fact that apparently irrefragible evidence can be produced by both protagonists: by Moutier, for example, the case of Levi,[2] in which Broca's area was destroyed by neoplasm in a right-handed man without any aphasic symptoms having been produced; and, again, the experiments by Burckhardt,[3] who removed from two right-handed dements the foot of the third left frontal convolution without producing the least trace of motor aphasia in either subject.

It may be mentioned here that slowly growing growths destroying the speech area, as in Levi's and Collier's cases,[4] should not be comparable in effects with sudden lesions.

Opposed to these contentions, however, is a vast number of cases, the majority of which have been carefully observed; for instance, the first cases recorded by Broca himself, in which there was complete motor aphasia due to a hemorrhagic cyst in the posterior third of the second and third frontal convolutions; an even more important case than this is that of Simon, in whom a complete inability to communicate except by signs was instantly induced by the traumatic destruction of the left third frontal convolution.

It is not necessary to expand here the number of apparently indubitable cases capable of being cited both for and against the idea that Broca's area is in right-handed persons the brain center specialized for the government of the function of motor speech. It suffices to say that there lay to the hands of Marie and Moutier much evidence which bore heavily against the topographical notions then prevalent, and to remind ourselves that Moutier cites freely cases of right-handed right hemiplegics without aphasia and also cases of left-handed left hemiplegics without any disturbance of their power to converse. Further, the strongest evidence at Moutier's disposal consists of certain patients who might be called, in Bramwell's phrase, cases of crossed aphasia—eccentric combinations of right hemiplegia with aphasia in left-handed individuals, or left-sided palsy with aphasia in right-handed persons.

These cases were used by Moutier to disprove the validity of Broca's area as a special speech center, but in reality, as shall be suggested later, they only impugned the theory of constant conjunction in any one subject of right-brainedness and left-handedness or left-brainedness and right-handedness.

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[2] Loc. cit., p. 102.

[3] Loc. cit., p. 103.

[4] Collier, Lancet, 1899, p. 824.

To account for these anomalies there was born of Marie and Moutier the idea that not the area of Broca but the much wider lenticular zone was responsible for language control; a proper scorn is thrown on the clinician who, confronted by a third left frontal convolution destruction in a patient who in life had never been aphasic, falls back feebly on the theory that the said patient must have been left-handed either without self-knowledge of the fact or at least without its discovery by others. However, a language center or intelligence center postulated in the lenticular zone still does not rid us of the difficulty, more especially if the said zone be found structurally normal, as the classicists aver frequently to be the case. Also the clearly cut cases cited by the older writer are not explained away even after the expenditure of much industry and ingenuity.

The conviction grows, therefore, that there is truth in both dogmata, but that adequate explanations of many anomalous cases cannot be given without the injection into the argument of some new factor not as yet brought under scrutiny.

In the most tentative fashion I want to suggest here that the simple statement that a given patient is right-handed or left-handed is not adequate in the light of some cases to be mentioned later. No more information than is contained in this somewhat bald announcement is made by any of the writers on this topic, saving Byrom Bramwell,[5] yet it would appear that not only by investigating the question of a patient's handedness but also that of the prevailing type of handedness in his stock, will we be able to throw some light on a very obscure chapter of neurological medicine.

Case I.—My first case is that of massive injury (bomb wound) of the right temporosphenoidal and occipital lobes in a left-handed man without left-handed relatives or ancestry. No aphasia.

This patient was wounded on August 15, 1915, near Arras, and admitted to the Hôpital Militaire, Ris Orangis, on September 25. He stated that when making hand grenades he suddenly became unconscious, but he remembered dimly being bandaged in the trench and being carried to the second line. He rapidly recovered complete consciousness and never lost it again. On August 7 he was operated upon at Houdain. No convulsion nor headache. Never any difficulty with speech. His left arm and leg felt as though they had been slept on (comme s'il avait dormi dessus). This improved, but was present on admission to the Ris Hospital. He never had had pain in the affected limbs. On September 5 he said he felt very well. There was an infected wound in the right temporal and lower temporoparietal region. Its upper portion was clean, with a granulating surface measuring 8 by $2\frac{1}{2}$ cm. In the posterior margin of the wound, behind the ear, there was a sinus about 5 cm. long, which extended inward and forward parallel to the external auditory canal. There was a marked bone defect, and the brain pulsated in the granulating area.

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[5] Lancet, 1899, p. 1473

Examination showed pupils equal with brisk reactions; sight emmetropic on left side. The right eye was myopic by four diopters. Left homonymous hemianopia complete to fixation point.

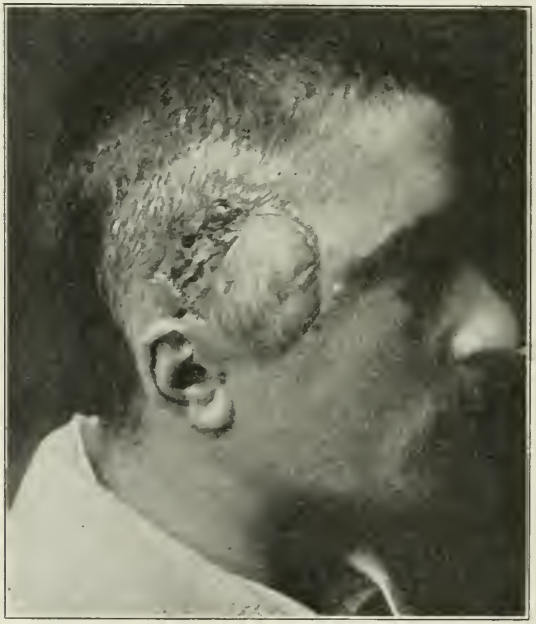

FIG. 1 (Case I).—Showing extent of wound.

Optic discs: The left showed venous tortuosity. The physiological pit was filled in and the left upper temporal quadrant was obscured by slight swelling. The right fundus showed no papilledema.

One may point out here that the formation of the myopic eyeball is such as to permit rapid drainage of fluid accumulated at the nerve head; as a consequence of this, papilledema is not a usual occurrence in myopic eyes. The presence of unilateral myopia in this patient probably accounts for the unilateral fundus changes. There was no nystagmus, diplopia, or strabismus. The lower jaw, on opening the mouth, swung to the right side, this being due not to a lesion of the motor root of the fifth nerve, but to fracture of the zygoma.

The general hypesthesia of the left side was seen in the face as elsewhere, but there was no localized fifth-nerve palsy. The left lower face was distinctly paresed for both voluntary and emotional movement, thus showing damage respectively to the right facial cortical and the right optic thalamus.

The right membrana tympani had been ruptured and hearing proportionally diminished in the right ear. The tongue swung markedly to the right on protrusion. The swinging of the lower jaw to the right had overcome the tongue's hemiparetic tendency to go to the left. Palatal movements were quite normal.

Motor system: there was distinct and general softening and shrinking of the muscles of the left arm and leg, there being a difference between the left and right upper arm of 2.5 cm.; between the legs of 2 cm. No tremor or athetosis. Slight ataxia of the sensory type existed in the left upper extremity. The weakness in the left arm was more marked than in the left leg, though proportionately less marked than that in the left face. He could not stand on the left leg alone.

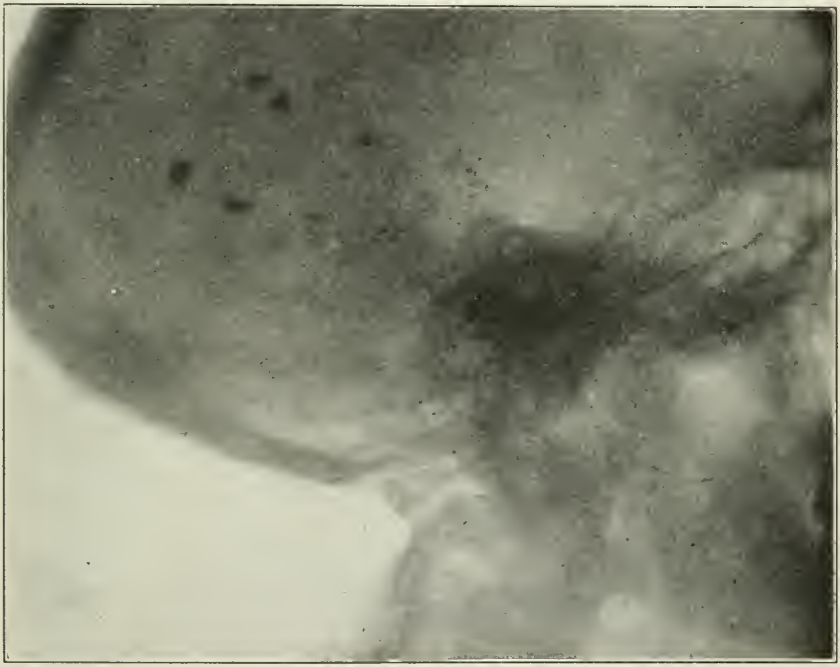

FIG. 2 (Case I).—Showing large bone defect and wide distribution of fragments of grenade and bone in the temporo-occipital area.

There was considerable titubation, probably the result of a lesion of Turck's bundle, uniting the temporal region to the pons. A distinct lowering of touch and superficial pain and deep muscle pain sensation existed over the whole of the left side of the body.

No mistakes were made in sense of position nor in the discrimination of temperature. Some slowness in the recognition of unseen objects held in the left hand, but in this regard also no mistakes were made.

Reflexes: All deep reflexes on the left side were exaggerated in degree. Abdominal reflexes were present on the right and absent on the left side. Plantar reflexes: right flexor, left extensor.

This patient was an intensely left-handed man, using that hand habitually for all complex acts. He had no motor speech difficulty whatsoever; no word deafness; he named promptly and accurately objects of which he had visual recognition. He had no apraxia or alexia. His memory was good. He read and wrote in a manner only interfered with by the complete hemianopia, of which mention has already been made. His father and mother were both right-handed persons. He was an only child, and knew of no other left-handed persons in his connection.

The chief point of interest in this patient seems to lie in the fact that he was left-handed to an extraordinary degree; he reversed the usual position of the knife and fork, and, while he wrote with the right hand, he was equally able to do so with the left.

Under these circumstances it would have been justifiable to have looked for a correspondingly marked disturbance of speech manifested in him as a result of the massive injury sustained by the right temporosphenoidal lobe. This injury not only was inflicted directly on the latter, but the fragments of the grenade and of driven bone are seen roentgenographically to have been flung through the cortex and to have become embedded in the right occipital pole.

The symptomatology here manifested has been presented in some detail in order that there may be shown the extensiveness of the disorganization of widely separated areas in the right brain. We are, therefore, not straining our postulate if we suppose that in this case we have to deal not only with an injury to the right transverse gyri of Heschl, but also with one affecting the commissural fibers between them and the homolateral half center of vision.

In the descriptions of the type of speech defect consequent upon temporal lesions there has been much fluctuation of opinion. Even the most recent text-books reproduce the idea that word-deafness is characteristic of lesions in the speech area of these regions, ignoring the evidence which goes to show that only the most sudden catastrophe successfully destroying at a blow the transverse gyri will produce such an aphasic extremity. The intermediate defects produced by disease processes are manifested, not by a cleanly cut inability to comprehend heard words, but by a depression of power to recall words voluntarily, especially the names of persons, places, and things.

To this phenomenon is usually added that of failure to name an object of which there is visual recognition. These two defects are, at first sight, almost of identical nature and origin, but it may be pointed out that the former depends on a depression of function in the cortical area containing the memories of words, while the latter arises from an interruption of the subcortical fibers uniting the visual and auditory centers.

In this patient, then, we have, to a maximum degree, an injury which, according to the teachings both of the classicists and their assailants, by its rapidity and extent, should have produced a maximum disorder of speech. There was no disorder.

In the literature of aphasia one finds that but few cases disagree with the general hypothesis that in right-handed persons the centers of language are situated on the left side of the brain. In a few instances in which aphasia has resulted from injury to the right brain some anomalous and adventitious circumstance has usually been brought forward to account for the situation. For example, it was found by Oppenheim[6] in two cases of affection of the right temporal convolution that in one there was acquired left-handedness in a woman, aged fifty-nine years, who had been found to use her left hand for all purposes owing to injury at the age of seventeen years; in the other case there were two tubercles in the right temporosphenoidal lobe, and aphasia is reported only to have appeared when the patient was already moribund, and, according to Oppenheim's assumption, as a result of toxic action on the auditory center in the left side of the brain.

Again, Long,[7] after describing a case of embolic right-sided hemiplegia with sensory aphasia in a left-handed woman in whose brain was found a wide-spread destruction of Broca's area and annectant gyri, accounts for the absence of motor aphasia symptoms by the hypothesis of an immediate assumption of speech function on the part of the uninjured hemisphere, as casuistic a theory as can easily be found even in the literature of this somewhat nebulous topic.

No such peculiar or recondite data are obtainable in this case to account for the escape of speech faculties supposedly resident in a portion of highly damaged brain tissue. In view of the seriousness of the lesion it is only possible for us to suppose that the patient's immunity from this disaster lies in the fact that, despite his left-handedness, he is also left-brained. An adumbration of why this may be so is the *raison d'etre* of this discussion.

The second case to which I wish here especially to refer is one published by Byrom Bramwell.[8]

Case II.—A man, aged thirty-six years, suffered from embolic right-sided hemiplegia and aphasia. He was left-handed and had been so all his life. He did everything but write with his left hand. None of his near relatives or ancestors were known to be left-handed. He was a twin; his twin brother was right-handed. The explanation given by Bramwell of this individual's peculiar reaction to his vascular accident is that, in spite of his left handedness, the left brain was educated as a speech area by reason of his having been taught to write with his right hand. However, I would point out that perhaps not sufficient weight is given to his isolation as a left-handed person in a stock entirely right-handed; and also that Bramwell's theory does not explain such cases as that reported by Senator:[9] an embolic left hemiplegia with aphasia in a right-handed individual. It is most unfortunate that it was impossible for Senator in the case of this woman to discover whether or not her stock contained a left-handed strain.

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[6] Quoted by Bruns in Geschwülste des Nerven systems.

[7] L'Encéphale, 1913, viii, 520.

[8] Loc. cit.

The third case was seen by me in the New York Hospital—a completely left-handed man in the service of Dr. Charles Gibson, with whom I saw him in consultation. He had sustained a fracture in the right occipitotemporal region with right middle meningeal hemorrhage.

Craniectomy had been performed, a bone defect of two by four inches having been made over the affected areas.

Following the injury the patient had suffered a left hemiplegia, from which he had recovered at the time of my examination. At intervals, however, he suffered from severe left-sided convulsions.

Despite his left-handedness, which was complete except for writing, associated with a severe injury to the right brain, he never had had the slightest interference with the function of speech.

This patient's relatives were all right-handed. He had lived, as had the French soldier whose condition was first described, as a member of a village community, in which, in both instances, were included many of their relations. Each man was quite positive that he was the only left-handed member of his stock.

We have now considered three cases of left-handed persons in whom brain injury produced phenomena opposed in their combinations to what we should expect in the light of our usual teachings. It is proper, then, to consider a like number of right-handed individuals showing similar peculiar results from similar cerebral catastrophes.

One may point out that, in the first set, our evidence as to each patient's variation from his stock-handedness must be of a negative character; but in the three cases now to be described, each right-handed individual can designate specifically relatives individually peculiar in that they differ from ordinary mankind in using their left hands for all complicated activities.

The first of this second series (Case 4) is that of a right-handed girl, aged twenty-two years, of whom I had charge in the service of Dr. James Taylor at the National Hospital in London. This patient repeatedly had severe attacks of Jacksonian convulsions confined to the left side of the body. These fits, occurring under observation over a period of twelve months, were always followed by a severe transient left hemiplegia and equally severe transient aphasia. The patient, herself right-handed, had a left-handed father and a left-handed mother, both of whom presented themselves for observation.

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[9] Charité annalen, 1904, xxviii, 150.

For the reports of the next two cases I am indebted to Dr. Charles Elsberg and Dr. E. D. Fisher respectively.

The history given by the former (Case 5) is that of a young man suffering from a right-sided deeply subcortical Rolandic glioma, on whom was performed at the New York Neurological Institute a right subtemporal decompression. He had complete aphasia for ten days following the operation. He was himself right-handed, but had two brothers both of whom were left-handed.

Patient.	Individual handedness.	Stock handedness.	lesion.	Physical results of lesion.	Speech.
Male, aged 25 years	Left-handed	Right-handed	Grenade wound right temporo-sphenoidal and occipital lobes	Left hemiplegia Left hemihypesthesia Left homonymous hemianopia	No disturbance.
Male, aged 36 years	Left-handed	Right-handed	Left brain embolus	Righ hemiplegia	Aphasia.
Male, aged 23 years	Left-handed	Right-handed	Right middle meningeal hemorrhage; skull fracture	Left hemiplegia Left-sided focal epilepsy	No disturbance.
Female, aged 22 years	Right-handed	Parents both left-handed	Right Rolandic tumor (gumma)	Left-sided focal epilepsy; transient attacks of left hemiplegia	Complete aphasia after each fit.
Male, aged 28 years	Right-handed	2 brothers, left-handed	Right subcortical Rolandic glioma; right subtemporal decompression	Slight left hemiplegia	Aphasia.
Female, aged 67 years	Right-handed	Mother, brother, daughter all left-handed	Right brain hemorrhage	Left hemiplegia	Aphasia.

The last case (Case 6) is that of a woman, aged sixty-seven years, under the care of Dr. Fisher. She had sustained a cerebral hemorrhage, as a result of which she had a left hemiplegia and a considerable degree of sensorimotor aphasia. She was right-handed, but her mother had been left-handed. She had a left-handed brother and a left-handed daughter.

The reasons why 95 per cent. of the human race are right-handed have been debated without definite conclusion for the past thirty years. An enormous number of theories have been elaborated, and to almost all of them many objections can be raised.

Barnes[10] is content to say that right-handedness is essentially hereditary, while Gowers[11] quotes the amazing notion that insofar as the human family took origin north of the equator, our first ancestors, seeing the sun travel from left to right, through manual demonstration of the fact and graphical reproduction of it, would naturally lay down in themselves the primitive elements of dexterity. Almost as difficult of proof are the hypotheses which endeavor to explain our asymmetry through the different widths of the carotids, the different blood-pressures in these vessels, and their differences in anatomical origin.

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[10] Lancet, 1903, i, 331.

[11] Lancet, 1902, ii, 1719.

Schaeffer[12] reports five right-handed cases, all with visceral transposition, as evidence against the theory that the right-sided position of the liver should inevitably make us more ready to employ the homolateral arm and hand.

Also Bastian's statement[13] that the specific gravity of the left brain is greater than that of the right, has not met with corroboration and if it had been confirmed, would not materially assist in laying bare the underlying factors of the condition.

Dareste[14] has advanced an interesting hypothesis to the effect that the embryo, applied first to the vitellus by its anterior surface, invariably turns on itself and becomes applied, in the majority of cases, by its left side. He asserts, with little enough proof however, that in this way development of the left side is impeded.

An almost identical theory is put forward by Brandt,[15] and a parallel idea from a strange source, that of the aborigines of North Queensland, is to the effect that right and left-handedness depends entirely on the side of the mother to which the infant presents at the moment of birth.[16]

It is apparently certain that all animals, notably the anthropoid apes, are either handed, and from protopaleolithic implements found in France and Kent it would seem that among our primeval forebears the domination of the left hand was as usual as that of the right.[17] The directions of the flakings on primitive meat and corn crushers of the neolithic period would seem to point to the same conclusions. A gradual recognition in the minds of the earliest men of the necessity of shielding the heart may have led to a tendency to right-handedness which has been transmitted to the bulk of the human family.

Stier[18] in 5000 soldiers found only 4.6 per cent. left-handed, but in over 60 per cent. of these there was obtained a very definite history of a sinistral tendency in the stock of each individual examined.

The percentage of cases in which this left-handed trend is present in the forebears must be—and this also is affirmed by Stier—very much larger than can be easily proved by direct statistics.

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[12] Berlin. klin. Wchnschr., 1911, No. 7, p. 295.
[13] Jour. Ment. Sci., 1866, p. 28.
[14] Bull. de la Soc. d'anthropologie, 1885, 415.
[15] Biolog. Centralblatt, 1913, xxxiii, 361.
[16] Chamberlain, Science, 1903, xviii, 788.
[17] Astley, Lancet, 1901, i, 1246.
[18] Monograph, Jena, 1911.

It would appear, then, that from the cases reported that this trend when present in the stock may produce in the few right-handed individuals of the sinistral stock a condition of brain similar to their collateral relatives and ancestors, with the result that the speech area in such persons becomes developed in an ectopic position. Likewise a left-handed person occurring eccentrically in a right-handed stock is dominated by the trend of that stock rather than by his own individual peculiarities.[19]

These matters would seem to be of small enough practical importance, but one may suggest that the considerations in favor of and against cranial operative procedures are not infrequently influenced by the fear of destruction of the areas governing the function of speech. On this account, apart from the academic interest of the question, it behooves us to record any facts seeming to assist us to increased accuracy of endeavor.

CIRCUMSCRIBED CYSTS OF THE LEPTOMENINGES, WITH THE REPORT OF A SUCCESSFUL OPERATIVE CASE.

By Frederic M. Hanes, M.A., M.D.,
PROFESSOR OF THERAPEUTICS, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA.

AND

A. M. Willis, M.D.,
CLINICAL PROFESSOR OF SURGERY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA.

Circumscribed cystic spinal meningitis is not an uncommon cause of spinal cord compression, and since operative interference offers prompt relief from an otherwise progressive and irreparable injury, its early recognition is of great importance. Among 45 cases operated upon for suspected tumor of the cord by Krause,[1] cystic meningitis or, as he terms it, arachnitis adhesiva circumscripta was found in 11, or about 24 per cent. Despite the fact, however, that cystic spinal meningitis can no longer be regarded as a rarity, the literature upon the subject is still very scanty and a general knowledge of the condition is lacking.

Spiller[2] wrote in 1908: "A collection of the clear fluid in a cyst of the spinal pia-arachnoid is a condition little known in America, as only one case occurring in this country is on record (Spiller, Musser, and Martin), and only a few are found in German literature. So far the French and English journals contain no examples." Since this was written several excellent papers have appeared. The first satisfactorily reported case was that of Spiller, Musser, and Martin,[3] in 1903. Since then instances of the affection have been reported by Krause,[4] Oppenheim,[5] Bruns,[6] de Montet,[7] Mendel and Adler,[8] Horsley,[9] Bliss,[10] Weisenburg and Müller,[11] Munro,[12] and Mills.[13] Krause, in his *Surgery of the Brain and Cord* (translation, Rebman, New York), gives very clear illustrations of the condition. That the disease is by no means so rare as the literature would indicate is attested by the experience of Munro,[14] who after reading the description of a case was able to report five instances from his own previous experience in which no satisfactory diagnosis had been registered at the time of operation. One unfamiliar with the condition might easily fail to recognize it at operation.

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[19] July 26, 1916. Man, aged thirty-one years. Seen in Bellevue Hospital. Almost complete palsy of left face and left arm, much weakness in left leg; left homonymous hemianopia; left hemianesthesia. Probable luetic cerebral thrombosis. Left-handed from infancy; prefers to write with the left hand. Never any speech difficulty even immediately following onset. Patient is the only left-handed individual in a family of seven, and in a large connection the members of which are well known to him.

[1] Surgery of the Brain, iii, 1055 (Rebman, New York).

[2] Am. Jour. Med. Sc., 1909, cxxxvii, 95.

Skoog[15] has recently reported two instances of leptomeningeal cysts, and reviews the literature. He makes the absolutely incorrect assertion that only four instances of simple uncomplicated cysts of the pia-arachnoid have been recorded, basing his statement upon what he terms a "thorough search of the literature." And yet the author fails even to mention the perfectly typical case that Weisenburg so fully recorded in this JOURNAL in 1910. Skoog apparently has undisclosed criteria of his own as to just what constitutes a leptomeningeal cyst, for he discredits Munro's five cases with the simple remark that "it is necessary to reject his reported cases." The unbiased reader of Munro's article will not, I think, feel the same necessity that Skoog so cryptically confesses.

Before proceeding to a discussion of circumscribed cystic spinal meningitis a very typical instance of the affection which recently came under our observation will be briefly reported:

CASE HISTORY.—*Progressive paralysis of both legs for one year; no pain; paresthesia of legs; anesthesia below mid-abdomen; bladder disturbances; operation and evacuation of localized leptomeiningeal cyst; marked improvement.*

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[3] Univ. of Penn. Med. Bull., 1903, xvi, 27.

[4] Verhandl. d. Deutsch. Gesellsch. f. Chir., 1907, xxxvi, 598.

[5] Beitrage zur Diagnostik und Therapie der Geschwulste im Bereich des Centralen Nervensystems, Berlin, 1907.

[6] Berl. klin. Wchnschr., 1908, p. 1753.

[7] Cor.-Bl. f., schweiz. Aerzte, 1908, p. 698.

[8] Berl. klin. Wchnschr., 1908, xlv, 1596.

[9] Brit. Med. Jour., 1909, i, 513.

[10] Jour. Am. Med. Assn., 1909, liii, 885.

[11] AM. JOUR. MED. SC., 1910., cxl, 719, No. 5.

[12] Surg., Gynec. and Obst., 1910, x, 235.

[13] Jour. Nerv. and Ment. Dis., 1910, xxxvii, 529

[14] Loc. cit.

[15] Jour. Am. Med. Assn., 1915, lxv, 394.

The patient, J. K., a colored man, aged twenty-six years, was brought to the Virginia Hospital because of complete paralysis of both legs.

The family and past histories were devoid of importance. He denied gonorrheal or syphilitic infection, and up until the present trouble had been healthy. No symptoms of tuberculosis.

About fifteen months ago the right leg began to grow weak and felt a little stiff. This was followed in a few weeks by similar symptoms in the left leg. His gait became unsteady and he staggered "like a drunken man." Three months after onset his legs had become so weak that he was forced to remain in bed most of the time. Except when assisted into a chair he has been in bed for the past twelve months.

The patient is positive that he has never suffered any pain during his present illness. No history of anything resembling root-pain can be elicited even with strong suggestion. He has had numbness of both legs from time to time, and is aware that the sense of touch is at present diminished in the legs.

During the past year he has had periods of frequency and urgency of urination, but has never been incontinent. At present he says he notices no abnormality of the bladder or rectal functions.

Physical Examination. The patient is a thin, poorly nourished man, lying in the dorsal decubitus, with both legs strongly flexed on the thighs. The head, neck, chest, and abdomen present no features of importance. No general or local adenopathy.

Neurological Examination. The pupils are equal in size, regular in outline, and both react actively to light and during accommodation. No nystagmus, strabismus, or diplopia. Vision good. Fundi negative. Hearing is acute and equal in the two ears. The other cranial nerves are likewise normal.

As the patient lies in bed the legs are constantly flexed, and upon the slightest stimulation they pass into a state of tonic spasm. All the muscles of the legs are involved in this spasm, and the abdominal muscles are rigid and spastic. Both legs are almost completely paralyzed; he can move them slightly after great effort, but cannot in any way control them. Upon attempting passively to flex and extend the patient's legs a condition of great spasticity is encountered which prevents any but the very slowest manipulations. The legs cannot be completely extended.

Sensation to touch, pain, heat, and cold is deficient over the legs and trunk up to the level of the ninth dorsal skin segment. The upper thighs and trunk are not completely anesthetic, but the patient is able to indicate with constancy and accuracy the line below which sensation is impaired. On the legs and feet, sensation is practically abolished. The tests for muscle and joint sense are untrustworthy because of the great degree of spasticity, but from passive movement of the toes it seems impaired.

The reflexes are normal in the upper limbs, but all deep reflexes are exaggerated in the legs. There is double ankle clonus, and the Babinski reflex is bilaterally positive. Because of the board-like spasticity of the abdominal muscles the superficial abdominal reflexes cannot be satisfactorily tested.

There is no sphincter disturbances at present. The patient is completely bed-ridden. The temperature and pulse are normal.

A spinal puncture was performed and 8 c.c. of fluid under apparently diminished pressure was obtained. The fluid had a distinct yellowish tinge, though not frankly yellow in color. The cell count showed the presence of three lymphocytes to the cubic millimeter. The Noguchi globulin reaction indicated the presence of a very marked excess of protein material. With the heat and acetic acid test a heavy, floccular precipitate formed in the fluid. The significance of this picture—xanthochromia, protein excess with low cell count—has been discussed recently by one of us in this Journal (Hanes, 1916, clii, 66). Suffice it to say that its presence strengthened the probable diagnosis of spinal cord tumor. The Wassermann reaction was negative in both blood and spinal fluid.

The clinical diagnosis of extramedullary tumor compressing the spinal cord was registered, and under ether anesthesia laminectomy was performed. The dura was exposed at the level of the fifth, sixth, and seventh dorsal vertebræ. It did not pulsate. Upon opening the dura at the level of the sixth dorsal vertebræ a cherry-sized translucent, delicate-walled cyst presented at once in the dorsal incision. This was incised with the escape of perfectly clear, colorless fluid, and the cyst structure collapsed. There was apparently only one cyst. The spinal canal was explored thoroughly above and below, but no other tumor mass could be found. The cord seemed flattened and somewhat compressed by the cyst, and the vessels below the level of the cyst were distinctly engorged and tortuous.

The dura was sutured and the wound closed. Healing was rapid, and on the eighth day after the operation was complete.

The improvement in the condition of the patient was immediate and quite remarkable. On the day following the operation he could move the legs with considerable certainty, and this improvement continued until on the tenth day following the operation he was able to stand for a moment or two alone. Since this time there has been a gradual gain in the strength and control of the legs, but improvement has been slower than perhaps would have been the case had the patient's circumstances permitted efficient physical therapy. The muscles of both legs are still spastic, though much less so than before operation, and the Babinski reflex is still bilaterally positive.

Six weeks after the operation lumbar puncture was again performed. The fluid was now quite normal in appearance, without a trace of color. There were four cells to the cubic millimeter, with only a faint trace of proteid, as contrasted with the former great excess. This finding proves incontestably that the xanthochromia and protein excess present in the spinal fluid before operation were caused by the cystic tumor which had formed a cul-de-sac below its site of growth. Upon restoring the integrity of the canal the fluid promptly resumed its normal character.

The exact etiology of circumscribed cystic formations in the spinal leptomeninges is uncertain. The pia-arachnoid spaces of the brain and cord form a true serous cavity analogous to the pleural and peritoneal spaces, and it is reasonable to assume, in view of the frequency of inflammatory adhesions in other serous cavities, that the delicate leptomeninges, as the result of either septic or aseptic inflammatory processes, form adhesions which may produce single or multiple cysts. The histological structure of the trabeculated pia-arachnoid membrane would seem to favor such a process. The occurrence of aseptic meningeal inflammations of various degrees, from meningismus to true purulent meningitis, with thousands of leukocytes in the spinal fluid (Zabel[16]), is not sufficiently recognized. Such aseptic inflammatory processes might easily lead to leptomeningeal adhesions and cyst formations.

Trauma has closely preceded the development of certain cases of cystic meningitis, and several writers mention it as an etiological factor.[17] [18] [19] We are inclined to believe that traumata by the production of small hemorrhagic effusions into the leptomeninges may cause toxic inflammation, with consequent adhesions. That inflammatory processes in structures in the neighborhood of the pia-arachnoid, such as spinal tuberculosis or osteomyelitis, may ultimately lead to localized leptomeningitis is well recognized. In general it seems fair to say that any process, either septic or aseptic, which causes localized meningeal inflammation, may through the formation of adhesions, produces cysts of the pia-arachnoid.

The pathological condition, as seen at operation, consists in the presence of one or more cysts, with very delicate walls. When the dura is incised the thin-walled, translucent, cystic structure protrudes under the pressure of the contained fluid. Upon puncturing the cyst the walls collapse and become inconspicuous. If in opening the dura one should puncture the pia-arachnoid cyst it is easily understandable that the condition might pass unrecognized. Certainly from some of the descriptions published, where "upon opening the dura a large quantity of fluid escaped under pressure," one is forced to conclude that a cyst was opened along with the dura.

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[16] Mitt. a. d. Grenzge. d. Med. u. Chir., 1913, xxv, 211.

[17] Mendel and Adler, loc. cit.

[18] Horsley, Victor, loc. cit.

[19] Bliss, M. A., loc. cit.

The cord shows the effect of the pressure which the cystic tumor has exerted, being somewhat flattened and compressed, with engorgement of the pial vessels. In our case the veins of the cord distal to the site of the cystic obstruction were markedly congested and tortuous, and we are convinced that this obstruction to the venous flow of blood accounts for the curious condition of the spinal fluid found in this case. The fluid was yellowish, with only 3 cells to the cubic millimeter; but it contained an enormous excess of protein, and coagulated on standing. In short, the fluid obtained by lumbar puncture had the characteristics of a transudate such as is commonly encountered as the result of venous obstruction. Spinal fluids with the characteristics just described are not at all uncommon, and are of very great practical significance, for they always indicate compression of the cord with the formation of a lumbar cul-de-sac.

The symptoms of circumscribed serous meningitis are those of cord tumor. We doubt the possibility of making a differential diagnosis between extramedullary tumor of the cord and cyst of the pia-arachnoid. Cysts, indeed, when circumscribed are tumors capable of exerting pressure which causes almost complete transverse blocking of the cord functions. We have never seen more intense spasticity or more complete paralysis than was present, for example, in our case, even in long-standing cases of extramedullary neoplasm.

Horsley[20] enumerates some eight differential points which he thinks are of service in the diagnosis of circumscribed serous meningitis. Horsley, however, has included in his paper certain cases which cannot properly be regarded as instances of circumscribed cystic meningitis, but are rather examples of meningomyelitis. Aside from this, moreover, one of us while working at the National Hospital for Paralyzed and Epileptics in London had the opportunity of studying carefully a case of circumscribed cystic meningitis which violated practically all of Horsley's differential points. Horsley operated for cord tumor and found a circumscribed cyst. Oppenheim[21] thinks cysts of the pia-arachnoid cannot be differentiated from extramedullary neoplasms. Fortunately, the need of separating the two conditions does not exist, for both demand precisely the same operative treatment. It is far more important to recognize that both neoplasms and cysts may present most atypical pictures and not to be misled thereby.

The symptoms and signs as reported by various observers consist of pain, disturbances of sensation, paralysis or paresis, abnormality of the reflexes, and sphincter disturbances. These are manifestations of transverse lesions of the cord from whatsoever cause, and in diagnosis one must eliminate syphilitic and tuberculous disease, acute meningomyelitis, extramedullary tumors as well as traumatic injuries, such as fracture dislocation of the vertebræ. In the process of differential diagnosis a thorough examination of the spinal fluid is of the greatest value. It is impossible to agree at all with Munro[22] when he states that "nearly every writer condemns lumbar puncture . . . as an aid to diagnosis except negatively." As we have shown in our case the condition of the spinal fluid was of the greatest positive support in the diagnosis of cord compression as opposed to meningomyelitis, gumma, or parenchymatous cord lesions.

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[20] Loc. cit.

[21] Lehrbuch der Nervenkrankheiten, 1913, i, 388 (full literature).

Pain has been a prominent feature of most of the cases recorded. Our patient denied absolutely having suffered any pain at all. Pain was formerly regarded as an essential clinical feature of spinal cord neoplasms, but we now know that extramedullary tumors may exist with none or only insignificant pain. The same is doubtless true of cystic meningitis.

The treatment of leptomeningeal cysts is wholly surgical. The time is rapidly approaching when *exploratory laminectomy* will be resorted to with greater frequency than is done at present. The operation is a simple one, easily within the powers of any competent surgeon. The removal of the spinous processes and dorsal laminæ does not materially weaken the spinal column, and the operative wound heals promptly. It is, of course, unnecessary to emphasize that laminectomy should never be performed except with the support of a competent neurological opinion.

THE TREATMENT OF FRACTURE OF THE SPINE.

By Norman Sharpe, M.D.,

NEUROLOGICAL SURGEON, NEW YORK POST-GRADUATE HOSPITAL.

There has been such an advance in surgical methods the past decade that conditions which formerly did not warrant surgical interference are now being successfully treated.

The recent developments in cranial and in intestinal surgery are illustrative of the advances made in surgery in general. This is specially true of the progress made in spinal-cord surgery during the last five years. However, as in any new field, progress is hampered by the beliefs and practises of the past, and that has operated strongly against progress in the rational treatment of spinal fractures.

Fracture of the spinal column with damage to the cord or roots is considered, and rightly so, a most serious injury. Though the spinal cord is the best protected structure of the body, once the bony canal is shattered the cord is most susceptible to hurt, and its extremely low, or perhaps absent, regenerative powers makes it unique among the body structures. The integrity of the protecting bony canal once broken it becomes a menace by reason of fragments driven into the cord and by its inelasticity prevents the escape of inflammatory exudates, with resulting compression of the nerve fibers.

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[22] Loc. cit.

It is the advice and practise of a majority of surgeons that in fracture of the spine, with damage to the cord, without obvious deformity and determinable loose fragments of bone, the symptoms are due to contusion or laceration of the cord or hemorrhage, and that it is better to defer operation until the symptoms have come to a standstill; and that fracture with immediate and complete abolition of function below the lesion indicates division of the cord, and no operation is justifiable. This attitude is, I believe, most questionable, and cannot be defended on theoretical, experimental, or clinical grounds.

In the discussions that have gone on in late years as to the advisability of early operation in these injuries, the opponents of early operation have maintained that laceration of the cord cannot be remedied by operation, and that the nerve fibers, if severely injured, degenerate whether compression is immediately removed or not. That removal of pressure by early operation will not cause the already destroyed fibers to regenerate is true. But the opponents of early operative interference have apparently overlooked several important facts. That is, in fractures with damage to the cord, short of a complete transverse lesion, there are many fibers and tracts that escape injury wholly or in part. And there are other factors that will work harm to the nerve fibers in addition to the damage received at the moment of injury. If operation is not done, compression by bone, by hemorrhage, or the quickly following edema will destroy the already damaged fibers and involve many of the sound ones. Interruption of conductivity of nerve fibers after fracture does not necessarily mean that those fibers are destroyed. In practically every case of damage to the cord, short of complete lesion, many of the interrupted fibers will later functionate, and it is to preserve the integrity of the sound fibers and to give the best chance of recovery to the damaged but not destroyed fibers that early operation is urged. In former years laminectomy was a formidable procedure, and operation was delayed on this account. But at the present time the dangers of laminectomy in skilled hands is but slight in comparison to the possible benefits.

Fracture of the spine may be due to direct force, and in this case the fracture may occur in any part of the spinal column. But the more usual cause is indirect force, such as severe falls on head, shoulders, or buttocks, or, more commonly, violent flexion, extension, or torsion of the spine by extreme pressure. In these cases the fracture is usually located in the lower cervical region or in the neighborhood of the dorsolumbar junction. Dislocation may accompany the fracture and the displaced vertebra may remain in the abnormal position or spring back into its normal place. It is in fracture-dislocation that the most serious damage to the cord is done.

According to Pearce Bailey, in almost one-third of the cases of fracture of the spine the cord escapes injury. These cases are to be treated, as are skeletal breaks elsewhere, by immobilization, and are not of special interest to the neurological surgeon unless symptoms of cord or root involvement arise later, due to new-bone formation. Case I is a good example of this type of spinal fracture.

Symptoms of cord injury in fracture are due to the following factors:

1. To fragments of displaced bone causing contusion or laceration of the nerve fibers, or a narrowing of the canal by the fractured laminæ or a projection backward of a vertebral body, causing compression of the cord. In these cases the symptoms of cord injury arise immediately after the accident.

2. Hemorrhage either into the cord substance (hematomyelia), causing laceration of the fibers, or hemorrhage around the cord, either intra- or extradural, causing compression of the cord. In these cases the symptoms come on shortly, may be hours after the injury, and are usually progressive.

3. Edema both within and around the cord, causing compression of the fibers. In itself edema gives rise to symptoms that appear, like those due to hemorrhage, some hours after the accident, and these symptoms are progressive. This edema, present after every injury to the cord, and by its compressive effects so destructive to the nerve fibers, forms one of the chief reasons for early operation. Its power to harm has been overlooked in the past, and recent operations have shown that in many cases symptoms indicating injury or compression of bone are really due to the compressive and destructive effects of the edema.

4. Narrowing of the spinal canal at the site of injury by new-bone growth or the formation of scar tissue. Here the symptoms arise months after the injury.

These factors operate singly or in combination. It is only in rare cases and in the slighter injuries that these factors operate singly. In the majority of fractures of the spine, two or more, and at times all, of these factors are seen. That is, in fractures with laceration or compression of the cord by displaced bone there is usually hemorrhage in or around the cord, it is always followed by edema, and often later by narrowing of the cord space by new-bone growth or scar formation. However, in nearly every case one factor, such as compression by bone or hemorrhage in or about the cord, so predominates as to render the other factors negligible for the time being, though later these other factors will add their quota to the sum total of the symptoms and have a strong effect on the probable results. It must not be forgotten in making a diagnosis and determining the probable factor or factors in the causation of the symptoms that, as mentioned above, immediate interruption of conductivity, whether partial or complete, does not necessarily mean laceration of the fibers or tracts interrupted. In addition to the loss of function of the damaged fibers the shock or jar of the injury may cause an inhibition of function of the sound fibers, more or less complete for a variable period of time, with later an almost complete functional recovery of these fibers. So that a case in which the symptoms coming on at once may seem to be due to laceration of the cord by displaced bone may be really one of compression by hemorrhage or edema, the primary symptoms being due to a functional inhibition of the above type. If these symptoms occurred in a structure of greater reparative power than the cord, a delay in operation would be justifiable, in order to permit of recovery of the fibers from the initial injury; but delay, with tissue so feebly resistant as the cord in the presence of continued compression by bone, hemorrhage, or edema may work permanent damage.

FRACTURE WITH SYMPTOMS OF PARTIAL ABOLITION OF FUNCTION. In cases of this type there is partial and irregularly distributed motor paralysis with abolition of some of the reflexes and areas of anesthesia below the site of the injury and probable disturbances of sphincteric control. In these cases the symptoms are due either to contusion, laceration, or compression of the cord by the crushed vertebræ or to compression by hemorrhage in or around the cord.

Experimental studies of contusion of the cord show, in proportion to the severity of the contusion, disintegration of the axis-cylinder; but this is usually less marked than in cases of compression. In continued compression, in which the hemorrhage becomes an added element, the nerve fibers disintegrate and finally liquefy.

In partial lesions of the cord there are found destroyed, damaged, and sound fibers side by side. Of the destroyed fibers nothing is to be expected; they will not regenerate. The fate of the damaged and of many of the sound fibers depends on whether the factors producing the injury are temporary or permanent. These factors are compression by bone, blood, and the certain edema which appears after every injury to the cord. If this compression is quickly removed not only will the sound fibers be preserved, but functional and even anatomical repair will take place in many of the damaged but not destroyed fibers. But if compression due to any or all of the above-mentioned three factors is at all severe, and is allowed to continue for as short a period as four days, not only will secondary degeneration appear in the damaged fibers, but many of the sound fibers will also be involved.

The late John B. Murphy said: "In fractures without considerable displacement we are justified in assuming that the cord is not suffering continued compression regardless of the degree of paralysis; operation is not indicated. If this paralysis is due to laceration it will not be improved by operation. If it is due to contusion it will recover without operation."

This advice might be good if displaced bone was the only factor in compression. But it overlooks the factors of hemorrhage and edema which, unless removed by operation, augment and continue the initial compression. It is true that lacerated fibers will not be improved by operation. It is not for their sake early operation is urged, but to give the best chance of recovery to the adjacent damaged compressed fibers and to preserve the sound fibers.

In contusion, also, hemorrhage and edema, at least edema, are always present, and if not relieved early by operation, will increase the ultimate impairment.

Allen has demonstrated the baneful effects of this edema by the improvement following experimental incisions into the cord after spinal fracture in animals.

This condition of cord edema is analogous to that seen in the cranial cavity after fractures of the skull. And just as the urgency of the symptoms in fracture of the skull call not so much for the location of the fracture and determination of hemorrhage, but for the relief of the general intracranial pressure, so in spinal fractures the demand is for relief of intraspinal pressure; and this is even more important than in head injuries, for the so-called silent areas of the brain do not exist in the cord where serious damage to any part of the cord means permanent loss of function. The necessity of accurate diagnosis as to whether the damage is caused by contusion, laceration, or compression by bone, hemorrhage, or edema does not exist. The urgent indications are for "spinal decompression" by laminectomy with free opening of the dura, giving the cord fibers the best possible opportunity for repair. (See Case III.)

One stated objection to the early operation, or in fact to any operation in the absence of deformity, is that in many reported cases of early laminectomy little or no improvement followed, though no displaced bone was found; "and as the cord appeared normal, the dura was not opened." Such observations are similar to those regarding so-called cranial decompressions when the dura is not opened.

Compression of cord fibers by edema will not be relieved by the removal of the laminæ alone. And just as in head injuries, removal of bone will not relieve the intracranial pressure unless the dura is also opened, so in spinal fractures a free opening of the dura is most important and should always be done.

J. T. Bottomley advises in partial lesions of the cord that "if fingers or the roentgen-rays find no deformity of bone, then it is fair to assume that lesion is due to contusion, hematomyelia, or hematorrachia, and operation is not indicated," as "the blood will be absorbed in four to six weeks." But as cord fibers, if damaged and compressed, may degenerate in four days, the pressure of the hemorrhage present, augmented by the following edema, may cause irreparable damage to the injured fibers, and probably also to many sound ones, long before the blood clot is absorbed.

E. W. Taylor, who also says that the damage to the cord is immediate following the injury, and that delay in operation is advisable, reports a case, and exhibits the cord of a large extradural hemorrhage, with organization of clot and resulting compression, of which he says "that operation would have been of benefit." Then why advise delay until the cord is irreparably damaged, as a wait of only four days may cause degeneration of the compressed fibers.

Bottomley also says that in partial lesions of the cord, if after waiting (weeks or months) no improvement occurs, or if improvement occurs and then ceases or retrogrades, operate. And yet what can be done by a late operation, in the face of continued compression of the cord by bone, hemorrhage or edema, or by all three, over a long period of time that could not be better done and with more chances of benefit by an early operation? Case IV is an excellent example of this.

It is said by many surgeons that early laminectomy adds insult to an already damaged cord, and yet these surgeons advise in midcervical fractures, with danger of involvement of the fourth cervical segment, immediate operation to prevent respiratory troubles.

Immediate loss of power and sensation in parts of the body below the fracture points to laceration of a section of the cord. Here the indications are for an early operation not for the sake of the destroyed fibers, but with the view of warding off the compressive effects of the fast following edema, thus preserving the sound fibers and giving the best chance of recovery to the damaged but not destroyed fibers.

There are, however, many cases of a milder type in which there is no immediate loss of function. In these cases following the injury there are cramps in the legs, burning and tingling of the skin of the legs, followed by a progressive loss of power and sensation. In these cases the symptoms indicate not laceration, but compression of the cord by bone or hemorrhage.

The progressive march of the symptoms show, not a further narrowing of the bony canal, but an increase of the hemorrhage and arrival of the destructive edema. Here early laminectomy is imperative if we would save the cord, or parts of it, from permanent injury. Even if no hemorrhage is present there may be a backward dislocation of the vertebral body, so that the cord is "kinked" and the canal narrowed; even if it is impossible to remove the bone projecting into the canal the laminectomy gives the cord ample room to curve over it, and allows for the escape of inflammatory exudate. Case II well illustrates this "kinking" of the cord by a displaced vertebra. Operation should be done as soon as the symptoms of shock have passed away. Even if the symptoms of cord injury are but slight, if progressive, laminectomy should be done and the dura opened to allow of drainage of whatever hemorrhage may be present and to ward off by this spinal "decompression" the effects of the edema which invariably follows injury to the cord, and which is so destructive to the delicate fibers.

FRACTURE WITH SYMPTOMS OF IMMEDIATE COMPLETE ABOLITION OF FUNCTION. It is in this type of cases that the opinion of surgeons is most sharply divided as to the advisability of operative interference. Many hold that immediate complete motor and sensory paralysis, with abolition of all reflexes below the lesion and loss of sphincter control, shows a total transverse lesion of the cord, and laminectomy is unjustifiable and can do no good. This would be true did the above symptoms positively indicate, as they do in many cases, complete destruction of the cord. But there have been many cases reported in which all the above symptoms were present, and were considered complete lesions of the cord, in which later partial function returned even without operation, and many reported in which operation was followed by fair recovery. The Bastian-Bruns so-called law, which is that there is a total loss of tendon reflexes in complete lesion, is, as an aid in diagnosis, only of value in a negative sense. That is, the presence of reflexes makes it certain that there is not a total lesion, while the absence of reflexes is not proof that the lesion is total unless such absence is persistent. In many cases of partial lesion there is a total loss of reflexes for more than eight days; so that there are no symptoms short of a deformity at the site of injury so great as to show complete obliteration of the spinal canal, which prove a complete transverse lesion of the cord.

It has been regarded by many that complete abolition of function below the injury must indicate, if not laceration, at least most severe compression of the cord. This is by no means necessarily the case. Alan Newton has shown by experiments in animals that the spinal cord is extremely sensitive to light degrees of compression. He found that a glass rod gently placed on end on the exposed cord arrested conduction immediately. After removal of the compression, conduction returned after an internal varying directly with the duration of the compression, and the amount of interference with function remaining after eleven to fourteen days following experiment depended on the same factor. These results of Newton's experiments are in themselves a strong argument for the early operation, showing the beneficial effects of swift removal of pressure due to whatever factor.

Mixter and Chase report a case of fracture of the 4th, 5th, and 6th cervical vertebræ, with immediate symptoms of complete destruction of the cord. Operation was done twenty-four hours after the accident. Six days later sensation returned over the entire body. In two weeks there was some return of the reflexes and the patient finally recovered fair control over the bladder and fair use of the legs. Died one year after injury from pyelonephritis.

Guy Hinsdale reports a case of a woman with fracture of the 1st, 2d, and 3d dorsal vertebræ, and complete and immediate paralysis of the body below the nipples. Laminectomy four days later showed the cord was edematous and pink, and much fluid escaped. Three years later the patient could walk with assistance, had control over the bladder, and touch sense was normal on one side. It is the added pressure of this edema, as found in Hinsdale's case, that is so destructive to nerve tissue, and which is present after every cord injury, that may turn the scale and cause widespread destruction of the cord, and furnishes a chief reason for early operation.

Many surgeons hold that in the absence of bony deformity, as determined by the fingers and the roentgen-rays, and with complete abolition of function, while it does not prove complete destruction it is better to delay operation until the cord has had an opportunity to recover what power it can; and when improvement ceases to operate.

C. G. Cumston states as an aid to diagnosis that reactions of degeneration are absent in the paralyzed muscles in even severe compression as long as the fourteenth day, but if the cord is completely severed there is no excitability of nerves to the induced current after the fourth day. But this is of little value from the stand-point of treatment, for under severe compression, increased by the certain edema, the cord, certainly the damaged fibers, will degenerate in four days.

Bastian, Kocher and others have outlined symptoms which indicate complete lesion of the cord, but the cases described above and many others show that these symptoms do not prove destruction of the cord, and we cannot rely upon them. Kocher believes that operation is unjustifiable in case symptoms of complete lesion are present, and favors operation in partial lesion when symptoms have come to a standstill. But, as we have seen, the symptoms of complete lesion are not absolutely trustworthy, and delay in partial lesion may irreparably damage the cord. A much more rational stand is that taken by Dr. Walton, who says:

"Early operation will not only accomplish all that later operation will do for these cases, but will do it better." (See Case X.)

In my opinion early laminectomy in skilled hands is the best treatment by far in fracture of the spine with cord lesions, and the only contra-indication to operation is a bony deformity so great as to show beyond doubt that the spinal canal is obliterated and the cord hopelessly crushed.

The operation should be performed as soon as the patient has reacted from the shock and the site of the lesion localized. A free opening of the bony canal will relieve compression by bone, whether due to driven-in laminæ or a backward projecting vertebral body causing angulation of the cord. If a projection presses against the cord in spite of the removal of the laminæ, sufficient bone can be chiseled or rongeured away to give the cord ample room. A free opening of the dura will permit of removal and drainage of blood, and will offset the compression effects of the following edema. The dura may be re-closed or not, as indicated by the condition of the cord. In very many cases it is best left open. The technic of the operation is briefly as follows:

A single incision is made in the median line down to the tips of the spinous processes. The muscles are then incised close to the spinous processes down to the laminæ and the incision packed with hot wet gauze to check bleeding. This is then done on the opposite side and also packed. The laminæ are freed of muscle by a broad periosteal elevator the whole length of the wound on either side. A large self-retaining retractor is then inserted, which gives a good exposure and effectually prevents bleeding. The ligaments between the spinous processes are divided and the processes removed by large special rongeurs. The laminæ are now rongeured away out to the transverse processes, thus giving a good exposure of the canal and cord. The dura is always to be opened, and in many cases it is best to leave it at least partly unclosed. Opening of the dura and the arachnoid allows for escape of blood or edema, and if the cord is tense and swollen a small longitudinal incision in the posterior columns will afford drainage. A drain at either end of the wound extending to the dura, or at least to the bottom of the muscle wound, will provide an escape for the wound fluids. The wound is closed by a layer suture of chromic catgut and the skin with silk. A narrow posterior splint of plaster moulded to the spine will prevent movement of the trunk and give the patient much comfort. Drains and some sutures are removed on the second day and the remainder in five days.

What shall be done in those cases in which at operation the cord is found completely divided? It is almost generally agreed at the present time that cord fibers once severed do not regenerate. Murphy said that if the cord is severed, approximation will avail nothing. However, of the five cases reported of severed cords sutured, four were living several years after operation, while without suture no patient has lived over one year. The great improvement following suture, in the sensory and trophic disturbances, thus averting the terrible bed-sores, warrant suture for this alone. The writer believes that suture of a severed cord should be attempted, If the ends cannot be approximated and the lesion is in the dorsolumbar region an attempt should be made to unite the roots above and below the lesion, as suggested by Kilvington. This cannot be done in the upper dorsal or cervical regions because of the short course of the roots in the canal. (As examples of complete lesion see Cases VIII and IX.)

There are many cases seen of old fracture with cord lesion on whom, for various reasons, no operation was done or the operation was not completely successful. They present symptoms varying from simple foot-drop or spasticity of one extremity to paralysis with loss of bladder control. Many of these show increasing impairment of function due to late scar-tissue formation and collecting of fluid at the site of the lesion or to new bone growth. Many of these cases can be improved by operation even at a late date, and in some a brilliant result is secured. (See Case VI.) These patients should not be abandoned as hopeless cripples merely because a period of several months or even years have elapsed since the injury was received. Although operation will completely relieve but few of them, yet definite improvement may follow laminectomy even at a late date.

However, the many cases reported of benefit resulting from late operation when symptoms of progress cease or retrogression sets in only indicates the good that could be done by early operation, for the factors of continued compression, bone, hemorrhage, or edema that brought improvement to a standstill had certainly worked harm that would have been prevented by early operation. (See Case VII.)

Therefore, I believe that in every case of fracture of the spine with damage to the cord, excepting only complete obliteration of the bony canal, an early laminectomy is urgently indicated to relieve the cord of the damaging effects of bone-pressure, hemorrhage, and edema, and to give the nerve tissue the best possible chance for repair.

SUMMARY. *Reasons for and Advantages of Early Laminectomy.*

1. Relieves pressure from cord whether due to depressed bone or blood clots.
2. If fracture-dislocation, allow cord ample room, relieving pressure effects of angulation.
3. Provides drainage of the certain edema, which by its compressive effects is destructive to the nerve fibers.
4. Allows for drainage of hemorrhage, if present, the compressive effects of which may be so great as to permanently damage the cord.
5. In skilled hands, laminectomy is not a difficult or dangerous operation, and by doing it early the surgeon has given the damaged cord the best possible chance for repair.

The following cases, some of which were operated on in conjunction with Dr. William Sharpe, were selected as illustrating points emphasized in the text:

Case I.—Fracture dislocation of the 2d cervical vertebra without cord injury. No operation.

W. K., aged twenty years, fell two stories, striking on his head. Unconscious for a short time. Took a walk one hour after injury. Continued to work, with occasional pain in the head, otherwise no complaint. There was a definite deformity of the spinous process of the second cervical vertebra, and the roentgen-rays showed a fracture-dislocation of this vertebra. A plaster collar was applied and worn for some time. The only complaint at this time was some numbness and tingling of hands and legs. Reflexes were normal: no Babinski, no sensory disturbances, and no sphincteric trouble. Three years later he still was well.

Case II.—Fracture-dislocation of the first lumbar vertebra with angulation of the cord.

P. M., aged forty years, fell from a hand car, striking his back. No loss of consciousness, but he was unable to rise, and his legs felt numb and cold. Had pain in the dorsolumbar region of the spine, occasionally radiating into the thighs. Retention of urine. Seen two weeks later. Could flex and extend both legs weakly. Hypesthesia over both legs to the groin; no analgesia. The reflexes of the lower extremities were entirely absent and the abdominal reflex absent, but the epigastric was present. No Babinski or Oppenheim (rather remarkable). There was a marked "knuckle" of the spine, with displacement of the first lumbar spinous process one and a half inches to the left of the median line.

Operation. Laminectomy was done, removing the laminæ of the 12th dorsal and the 1st and 2d lumbar vertebræ. The first vertebra was found rotated to the left, so that the spinous process was one and one-half inches from the median line. The right lamina of this vertebra was fractured and separated from the spinous process. A mass of torn ligaments, muscle, and blood clot found in the space between the spinous process and fractured lamina pressing down upon the cord. The cord was sharply angulated by the projection backward of the dislocated 1st lumbar vertebra. The dura was freely opened and the arachnoid found balloned with fluid and the cord edematous. No hemorrhage was found. The dura was partly re-closed and rubber tissue drain passed down to the cord. The wound was closed by a layer suture of chromic catgut and a narrow posterior plaster splint applied; thirty-two days later he was walking with aid of crutches. Sensation was normal. Knee-jerks were still absent.

One year after operation he walks with spastic awkward gait, but without crutches or cane, and is able to work.

Case III.—Fracture of the lumbar vertebræ, with dislocation of the 3d lumbar.

P. P., aged twenty-seven years. Struck by an automobile. Brought to hospital in shock. Not unconscious. Could not move legs, but one hour later moved them slightly. Reflexes absent and hypesthesia to groin. Retention of urine. A definite depression found over the 3d lumbar vertebra. The spinous processes of the 2d and 4th lumbar vertebræ were palpable, but crushed into the laminæ. Had deep laceration of the perineum and sacral region. Laminectomy was done as soon as the patient reacted from the shock, several hours after the injury. The spinous processes and laminæ of the 2d, 3d, and 4th lumbar vertebræ were removed, disclosing a backward dislocation of the 3d vertebra, which reduced itself with a definite click and the rongeurs were inserted under the laminæ. There was a marked angulation of the cauda opposite the 3d lumbar vertebra. The dura was found distended and tense, but not torn. On incising the dura, blood-tinged fluid spurted to a height of seven inches. No definite subdural hemorrhage was found and no apparent lesion of the roots of the cauda. Dura partly re-closed and the wound closed by layer suture, with one drain at the lower angle. Recovery uneventful, though the laceration on the sacrum required dressing for two and a half months; patient fully recovered, and one month later walked with crutches. At the present time, fifteen months later, he is working and has no complaints. Babinski on left foot.

Case IV.—Old fracture of spine.

J. S., aged forty-two years; miner. Eighteen months previously, while mining, was struck on the lower back by falling rock. Not unconscious, but could move his legs only slightly. Was in hospital eight weeks; diagnosis: "sprain of back that would get well in time." No operation. Has since been unable to walk without crutches. Ever since leaving hospital has had pain, intense at times, in feet and legs. Retention of urine for eight days following accident, and dribbling for last four or five months. Examination eighteen months after accident showed exaggerated reflexes in lower extremities; a variable Babinski was more often present on the right side and scattered areas of hypesthesia and hyperesthesia on both legs. Both legs were spastic, with slight ankle clonus on the right side. Can move legs but weakly. Roentgen-rays showed deformed vertebræ at the lumbosacral junction.

Operation. Spinous processes and laminæ of the 4th and 5th lumbar and 1st sacral vertebræ removed. The bodies of these vertebræ were found crumpled together, with marked posterior displacement of the 4th lumbar vertebra, a portion of it protruding backward among the roots of the cauda, almost separating it in two portions. The dura opposite the 5th lumbar vertebra was thickened with many underlying adhesions, with a definite angulation of the cauda at this point. The adhesions were freed, the projecting portions of bone cut away and the dura re-closed. The wound was closed by layer suture of chromic catgut and drained by rubber tissue. Three days later he spoke of peculiar sensations in the toes and feet. Six months later he was doing light work in the mines. At present is doing work which requires standing, although not heavy work, using neither crutches nor cane.

Here an early laminectomy would have relieved the compressive effects of the fractured vertebræ and prevented the eighteen months' invalidism of the patient.

CASE V.—Fracture of the 1st lumbar vertebra.

R. L., aged four and a half years. When nine months old was struck by an automobile while lying in her coach. Since then she has been unable to use her legs and has had incontinence of the bladder and bowel to the present time. Examination at four and a half years showed slight motion in toes and feet, but they cannot be raised from the bed. Sensation only slightly impaired; no anesthesia or analgesia. Quite marked left dorsolumbar scoliosis.

Operation. The spinous processes of the 12th dorsal and 1st and 2d lumbar vertebræ were removed, revealing a marked posterior constriction of the spinal canal by the laminæ of the 1st lumbar vertebræ. The dura was opened, exposing a cord apparently normal. No evidence of hemorrhage or of scar formation. The dura was re-closed and the wound closed by layer suture.

No improvement noted as yet, six months after operation. In this case it is probable that permanent damage was done to the cord at the time of the accident. However, early operation would have removed the compression of the fractured laminæ and offset the following edema, and possibly preserved to her more function than shw now has.

CASE VI.—Old fracture of lumbar vertebræ.

C. M., aged eighteen years. Fell from a second-story window, striking on the back. Not unconscious. Unable to move the right leg. Roentgen-rays showed dislocation of the 2d lumbar vertebra. No operation. Plaster cast applied for two weeks. Unable to use the right leg. After one month the patient could walk with crutches. No bladder symptoms or sensory disturbances. As months went by some improvement occurred. She could walk without crutches, but with marked dragging of the right leg.

Examination six months after accident showed much atrophy of the right leg, especially in the extensors of the thigh. Slight foot-drop. Patient walked on the toes of the right foot and dragged the leg badly. No Babinski, Oppenheim, or clonus present. No disturbances of sensation. Definite hump on the back over the 2d and 3d lumbar vertebræ. Roentgen-rays showed dislocation to the left and possible fracture of the 2d and 3d lumbar vertebræ.

Operation. Median incision over the first four lumbar vertebræ. Spinous processes and laminæ of the 2d and 3d vertebræ removed, disclosing much scar tissue beneath. Body of the 2d lumbar projected backward, causing angulation of the cauda to the left. On incising the dura fluid spurted several inches. Roots of the cauda were found compressed between the scar tissue under the laminæ and the dislocated vertebræ. Removal of laminæ allowed ample room for the cauda. The dura was partly re-closed. Rubber tissue drain inserted and the wound was closed by the usual method.

Thirty days after operation patient has better use of the leg and walked with improved gait. Four months later there was marked improvement, which has continued to the present time. Ten months after operation patient walks with but slight limp, though there is still some weakness in the dorsal flexion of the foot.

Case VII.—Old fracture at dorsolumbar junction.

Mrs. J. C., aged forty-two years. Seven years ago fell on a step, striking the lower part of the spine. Immediately got up and walked for some distance home without much pain or difficulty. No symptoms until three months later. Then had difficulty in urination, which passed on to incontinence. The bowels became affected a short time afterward. At the same time there was twitching of the muscles of the left leg, and later partial paralysis of this leg with foot-drop developed. Eighteen months later the leg improved and partial paralysis with foot-drop developed in the right leg. She still dragged the left leg, but the right leg was the weaker. For the last five years she has been unable to walk alone.

Examination seven years after accident showed considerable motor power in the left leg, but drags the right leg and cannot stand alone. Pateller reflexes much exaggerated. Babinski on both sides and ankle clonus marked R>L. Slight but constant muscular twitching of the right leg. Hyperesthesia over both extremities, abdomen, and back. Considerable muscle spasm over the buttocks in response to stimuli. Serum and fluid Wassermann negative. Roentgen-rays showed thickening of the 12th dorsal and 1st lumbar vertebræ.

Operation. Median incision from the 11th dorsal to the 2d lumbar. Laminæ of the 12th dorsal and 1st lumbar enormously thickened, one-half to one inch in thickness, very vascular, spongy bone (callous formation). Beneath these laminæ was found a mass of scar tissue, one-half to three-fourth inches thick, pressing upon the cord and causing depression in the dura. On removal of this scar mass the dura rounded out; the cord appeared normal. The wound was closed in the usual manner; no drain.

Three months later there was a variable improvement noted; better some days, others not. Seven months later the patient could walk without support and with but slight spasticity. After riding 135 miles in a Ford car she was able to walk into the office. There is still present a double Babinski and vesical incontinence.

Case VIII.—Fracture of the 10th dorsal vertebra with complete lesion of the cord.

T. S., aged thirty-four years. Fell a considerable distance and was brought to hospital conscious, but with complete paralysis of the legs and all reflexes abolished. Anesthesia of both legs up to the iliac crests. Hypesthesia over area of the 12th dorsal segment one and a half inches above the ilium. Retention of urine. There was an easily palpable prominence of the 10th dorsal vertebra. Laminectomy was done when the patient had reacted from the shock, twenty hours after accident.

Operation. Median incision from the 9th to the 12th dorsal vertebræ. The interspinous ligaments were found torn loose between the 9th and 10th vertebræ. There was a posterior dislocation of the 10th dorsal vertebra, causing a marked angulation of the cord. The dura was tense and bulged through the laminectomy opening. The cord was immensely swollen and completely filled the dural sac. On opening the dura, blood-tinged fluid escaped and the cord appeared macerated, more in its left half, with small hemorrhages scattered over the surface. As the cord bulged markedly the laminæ of the 9th and 8th dorsal vertebræ were also removed and the opening in the dura was enlarged. There was no definite separation of cord fibers. The dura was left unclosed and the muscle wound closed in the usual manner with a drain.

Operation disclosed a severely damaged cord, but by relieving bone compression and by offsetting the pressure effects of the severe edema, gave the fibers the best possible chance for repair. Unfortunately on admission to hospital patient was catheterized by an orderly and developed a cystitis which caused his death eighteen days after operation.

In cases of cord injury it is wise to avoid, if possible, the use of the catheter. Repeated massage of the bladder sphincter through the rectum will usually relieve retention.

Case IX.—Fracture of the spine with complete lesion of the cord.

W. O., aged thirty-eight years. While intoxicated the patient, a very heavy man, fell backward from a fence to the ground. When brought to hospital he seemed to be merely drunk, but application of ammonia to the nose caused him to move his arms, but not the legs.

Examination of the back disclosed a definite hiatus over the 10th dorsal vertebra. When the effects of the alcohol had passed he was found to have complete paralysis and anesthesia of both legs to the waist. Complained of severe pain in the back over the lower dorsal spine. Laminectomy was done twenty hours after the accident.

Operation. Incision from the 8th to the 10th dorsal spines. There was a definite posterior dislocation of the 11th dorsal vertebra, with fracture dislocation of the 10th dorsal. On removal of the laminæ of the 9th, 10th, and 11th vertebræ much free bleeding was encountered in the region of the 10th dorsal vertebra, which was so severe as to require packing. On incising the dura much free blood escaped, revealing a complete separation of the cord for a distance of one and a half inches. The 10th dorsal vertebra was freely movable. Packing was required to control the hemorrhage. The dura was left unclosed. A drain was inserted and the wound closed by the usual method.

The symptoms in this case from the outset were those of complete cord lesion, but in laminectomy lay the only possible chance for relief. An attempt to suture the cord, or to unite the roots above and below the lesion, was rendered impossible by the extensive hemorrhage.

Death occurred on the twentieth day, this patient having also developed cystitis following unwise catheterization.

Case X.—The importance of accurate localization of the lesion and its difficulty in the absence of definite symptoms, especially in children, is well shown by the following case:

J. B., a child, aged seven years, suffered a fall, which showed no deformity of the spine, but caused complete paralysis of the legs and sphincter. Laminectomy done two days later over the 6th and 7th dorsal vertebræ showed no lesion of the cord. Seen by me seven months later the paralysis of the legs and sphincters had persisted in great part. The lesion was localized over the 3d dorsal vertebra. Laminectomy at this point showed slight thickening of the laminæ. Many adhesions between the cord and meninges, the large amount of fluid in the meshes of the adhesions giving it a cystic appearance and much yellowish scar tissue present (old hemorrhage). There has been, as was to be expected from the conditions found at operation, no improvement in this case, nine months after operation.

Early operation at the proper site would have removed the blood, offset the effects of the edema, and would doubtless have been of much benefit.

THE ETIOLOGY AND PREVENTION OF TUBERCULOSIS FROM THE SOCIOLOGICAL POINTS OF VIEW.

By William Charles White, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF PITTSBURGH; MEDICAL DIRECTOR, TUBERCULOSIS LEAGUE HOSPITAL.

The etiology of tuberculosis has not yet been solved. For thirty-nine years, since the wonderful discovery of Koch, we have known that no tuberculosis exists without the tubercle bacillus. This one great truth has been established, but it is not all the truth, for it is just as salient to say there is no tuberculosis without the animal body. Even these two great factors do not close the discussion, for some relation arises between the tubercle bacillus and the animal body, occasioned by their contact, which must attain before the essential feature of tuberculosis, the miliary tubercle, is formed.

THE TUBERCLE BACILLUS. From the time of the isolation of the tubercle bacillus by Koch, it has been studied in many ways. We know in part its form, singly and in colonies, its varieties, its chemical reactions and chemical compositions, its necessary food and environment, its excretions and enzymes, its life history, in glass and as a parasite, its resistance to light, to heat, and to chemicals, but not yet the one essential factor, why and how it produces a tubercle.

THE ANIMAL BODY. The study of the tubercle bacillus outside the body has been comparatively easy. The organism is, however, lost when we put it within the animal body. We know it soon enters a phagocyte cell, probably chiefly one of endothelial origin, but once inside of this cell, there begins a series of chemical and physiological changes, wholly obscure to us as yet. After some days, however, we see the evidence in the miliary tubercle, of the busy life it has led, marshaling against it at least three different armies of cells: polynuclear leukocytes, endothelial cells, and lymphocytes.

It is not surprising that our knowledge of etiology as it relates to the animal body is limited, for if we seek to reduce our size to that of a tubercle bacillus, retain our mentality, and start a wandering journey within the animal body we are soon lost in a maze of possible resting places. Before starting on such a journey we have the choice of several portals of entry, each leading to an environment in different organs and tissues of widely varying chemical structure. We see a chance of destroying sight with almost instant discovery, by establishing a solitary tubercle in the optic nerve, as opposed to the chance of establishing many thousands of tubercles, without discovery, within the lungs, or in a hidden lymph gland. But such choice of a final resting place is destroyed by the obstacles we meet on our journey, a blood current to carry us here or there, a wandering cell to transport us, a fixed cell to engulf us, an inimical fluid to dissolve us, it is small wonder all the truth has not yet dawned.

Our difficulties grow when we realize that we are just establishing our first firm basis for accurate physiological and chemical study of the animal body. Through the efforts of Fischer, Hoppe-Seyler, Folin, Mendel, Starling and many others we have realized that, first, an equilibrium must be established for the animal body, and, after this, an intake of known composition be added before resultant compounds can be determined. It is not strange when this knowledge is so meager that we have not discovered under what chemical condition of the body the tubercle bacillus can flourish.

INVESTIGATOR AND INVESTIGATION. One of our best students has recently said to me, "If I had the opportunity to study tuberculosis I would not know where to begin; it is like battling against the waves of the ocean." It is not so bad as this, however; what we need is a new grasp of our problem on a broader basis. The crux of the problem is the relation existing between the tubercle bacillus and the animal body.

New problems for research are opened to us daily by the surgeon, the anatomist, the physiologist, and the chemist, and probably many of these must be solved before the true etiological factors are apparent and relief from our suffering from this disease attained.

Pressing Problems. Such problems are involved in the answers to the following questions:

Why does the tubercle bacillus select the apices of the upper lobes of the lungs in man and the cephalic ends of the caudal lobes in cattle?

What is the relation of small doses of tubercle bacilli from various sources to later immunity and a reduction of morbidity and mortality?

What is the relation of early localized lymph glandular lesions to later more generalized tuberculosis, ranging from early lesions in the lungs to general miliary tuberculosis?

What is the chance of reaching the tubercle bacilli lying within tubercles in the body of an animal by chemicals introduced into the blood stream, and what hope does such study hold out of cure or arrest of the process?

What bearing has the physiology of various organs, such as the spleen, on the general problem of immunity to tuberculosis?

What hope have we of establishing immunity by vaccination or arrest and cure by immune sera? and so on, a host of unanswered questions bearing directly on our relief from the stand-point of control by social measures.

If we choose the lung as the chief point of attack in the animal body as the object of our study, we are conscious at once of a chemical factory to which every organ and tissue sends its contributions, through veins, lymphatic vessels and thoracic duct, contributions which vary all the way from the internal secretion of the adrenal glands to the neutral fats, changed by the lining membrane of the bowel and transported by the lymphatic channels from the food in the intestine.

Any one of these substances may contain the solution of the secret of the choice of this organ by this widely distributed bacillus.

If we seek to solve the question why tuberculosis attacks the apex of the upper lobe in man, one can see how complex even this question is when the following explanations of it are available for study.

1. That it may be due to mechanical pressure from rib and clavicle producing a quiet area; this, of course, is not applicable to the place of choice of the bovine lesion in the caudal lobes.

2. There may be a peculiar chemistry of the apices of the lungs in these two animals dependent upon position and directness of the blood stream or other similar factor, determining a peculiar quality of fluid or cell in this region.

3. There may be some peculiar anatomical relation existing between the portal of entry, the lymphatic glandular system, and various arteries which, by directness of stream and current, carry tubercle bacilli once entering the blood to these regions.

4. There may be some anatomical relation between the lymphatic system and these regions which carries to them tubercle bacilli entering the lymphatics.

Let me point out again the difficulties by taking the latter as an example. Only within one year has there been any accurate knowledge of the lymphatics of the lung and their relation to the intestinal lymphatics, and yet there seems much of evidence to prove that the tubercle bacillus has some definite relation to the endothelial cells of this vascular system.

These problems may be solved for us by the chemist, the physiologist, the surgeon, or by all combined.

What we especially need are funds and facilities to provide the opportunity for research and research workers to take up these problems.

THE SOCIAL AGENT. Our lack of specific knowledge can in no way be offered as an excuse for laxity in putting in operation the knowledge we already possess. Our various organizations (from national to local), the most efficient ever established against a single disease, stand as evidence that we have not shirked our duty.

Perhaps, however, our wisdom has not always been as prominent as our energy, and mainly we have failed to realize that our most efficient agents must always be doctors and nurses with a social sense. These alone can combine skill in diagnosis and treatment, with a knowledge of social conditions which underlie the spread of this disease.

One of the most disturbing features of modern work has been the gradual loss of respect for medicine and nursing as professions. This has become especially marked in tuberculosis work, where, with the establishment of laboratories, new agents of social service, and executive secretaries of organizations, the curious condition has arisen that there is a wide-spread opinion that little skill is necessary for the diagnosing and provision of consumptive people. There is scarcely a city or State today in which a layman operating as secretary or agent of a society for the prevention of tuberculosis is not able to both get the sputum analyzed and the patient placed in a hospital without ever having to see a doctor.

I often wonder whether our whole flimsy construction of medical and nursing training is not at fault when it is possible for laymen and laywomen to do the work which our present long course of training leading to degrees, licenses, doctors, and nurses to do.

Two great facts for some years have steadily robbed the race of the assistance of these two groups: (1) the exclusion of tuberculosis from the institutions of general professional training, and (2) the establishment of special institutions in territory inaccessible to students of these two great professions.

A new and healthy movement in America has lately been evidenced by the work of the Tuberculosis League in Pittsburgh, the Phipps Institute in Philadelphia, and Jefferson Medical College, in connection with the schools to which they are attached, in demanding practical experience in this work as part of the prescribed course.

I am convinced that the single factor of making the practical education of tuberculosis, from the stand-point of diagnosis, treatment, and social aspect, a demand of the prescribed courses for doctors and nurses in the institutions where they are trained will do more in five years to reduce the morbidity and mortality from this disease than all the special institutions for its care that we have been at such pains to establish.

THE SOCIAL FABRIC. How much of tuberculosis is closely bound up with our houses, our schools, our food, our workshops, our means of transportation, our dusty streets, our wages, our poverty, and with disease other than that caused by the tubercle bacillus, cannot yet be answered completely and finally. We know enough, however, to make these relations part of the education of our whole population.

For such education three great sources are always open to us:

The first and most important—the schools—is most likely to succeed because of the legal backing which makes listening and teaching compulsory.

The second, the pulpit. I never attempt a special lecture on this subject that my effort does not sink into insignificance beside those of my friends and coworkers in my own community. For instance, when Rabbi Levy, with his wonderful conception of the Fatherhood of God; Bishop Canevin, with his great and good paternalism; and Dr. McIlvaine, with his fearless and loving admonition, and many others, join on a chosen Sunday each year in teaching the truths of this great problem to their congregations I realize that a force for education has joined the ranks of our special organizations the world over that marks a most powerful ally in the direction of universal education of this subject.

The third great agent of education is the daily paper. I think all who know must feel disappointment with the help of these powerful agents. I suppose their sin is wrapped up with the fact that their papers must be sold. The selling agent is news, and not the reiteration so essential to education; but every once in a while the entrance of tuberculosis to the family of the throne room of the paper brings forth a new ally of wonderful power.

The essential feature of such education, however, must be truth. Each day reveals new evidences of sadness resulting from careless statements which lead only to fear and bring the suffering of the outcast to the consumptive populace.

The standardization each year of knowledge through some central office, like the Federal Government or the National Association, would tend to lessen the dangers of each successive period of advance.

Correlated Movements. Next to education there is not a movement for the health and welfare of the race which has not had its share in reducing this sickness—housing reform, child welfare, pure water, better wages, pure food, health laws, school lunches, ventilation, food lines—all aid.

I often wish to each might be given the credit for all it has contributed to the present great reduction in tuberculosis, for I sometimes fear that in our enthusiasm we have claimed too much and been misled by the establishment of institutions which, while necessary for housing this excluded portion of the race, have largely failed to rise above mere housing institutions and have neglected that perhaps more important foundation, provision for specific research in this work.

Perhaps one of the most striking conditions of modern municipalities is the large number of small charitable institutions, each with laundry, kitchen, bakeshop, purchasing department, engineering department, and high-priced superintendent and officers, to which the whole public gives more or less lavishly without any thought for economic and careful use of their funds. There ought to be some place, a legal authority, to stop such waste and carelessness and establish a central department, including laundry, kitchen, storehouse, and other such necessities for these smaller institutions for each community.

Many interesting social studies by Federal, State, and local organizations have been made. Among these are the housing surveys by Dr. Biggs in New York, the study of the children of the tuberculous, as compared with the children of the non-tuberculous and many others which need confirmation, with the eradication often of sources of error in the comparison of results which arise because of variation in technic.

Division of Labor. With such a universal problem and so great a host of agents entering into its solution, perhaps the two outstanding demands of this work are uniformity and equable division of the labor.

To what end is all our labor if one class is helped and another neglected; if one State is efficient and another lax; if one race is protected and another left to exposure?

As it appears today the poor receive a large percentage of our beneficence while the great middle class suffers for its independence by our neglect, and the rich wander from climate to climate and doctor to doctor, hoping that God in His goodness has vouchsafed some knowledge for their benefit which can be purchased with gold and silver to the exclusion of the rest of the world.

Or, again, one State provides lavishly for this one feature of public health while a neighboring State, separated from it by an imaginary line, turns its back upon its duty; or one town attempts efficient handling of its problem while a nearby borough does nothing. The source of such discrepancies, of course, lies where the law originates in the State and Federal Government.

RELATION TO OTHER HEALTH MOVEMENTS. When such a law is at last prescribed we are apt to make again the mistake of separating tuberculosis from other health and charitable activities, and so waste a great part of the efforts of our agents by reason of a duplication of labor.

THE SOLUTION. I am more and more convinced of the soundness of the solution for this problem which I have offered on more than one occasion, and inasmuch as I believe in it so fully, I am to be guilty of proposing it again to you.

This plan is based on a study of our solution of a similar universal problem presented by our educational demands.

Emanating from State law there is in general established in educational work a unit equipment for a unit of population. By this equipment is gained a uniform compulsory and intensive application of the law to all concerned. The money for the expense of this care is provided by State and local taxation, determined largely by the density of population and the need of the community. Those who are interested in this phase of the question would do well to read Cubberly's *Problems of State and Municipal Education.*

In the educational field there has gradually developed a knowledge of the equipment necessary for a given population, and this equipment has been apportioned so as to be easily accessible by those whom it is to serve. The management of these units is centered in a legally constituted governing body, which also controls the expenditure of the funds collected by taxation.

The same form of control is applicable throughout to tuberculosis and other health problems.

In the first place, our statistical studies have given us fairly accurate knowledge of where to place our equipment and of what the equipment should consist.

I should say that for each hundred thousand population there should be a hospital of 200 beds, a dispensary and an open air school. There should be fifteen nurses, of whom five are visiting social service nurses and four or five physicians. Such an equipment might easily expand and include all public activities, child welfare, pneumonia, syphilis and other health and public welfare problems.

The expense should be borne as the educational expense is borne, and the demand made mandatory by state law.

Large centers of population would be looked on as but the multiplication of units of 100,000, and the equipment would be multiplied accordingly, just as we now multiply our school equipment. Each unit would be self-governing, but centralized in some central governing board which would establish the uniformity of the work and the prevention of overlapping.

The State that sees fit to establish such a principle will, it seems to me, soonest reach the land of heart's desire, and will have a machinery as elastic as the problems to be dealt with, a machinery that can grow as knowledge grows and retract or reconstruct as necessity decreases, a machinery that can be used as a teaching center for doctors, nurses, and social agents, and the sooner it comes, the sooner will we see spelled on the wall the doom of our present boarding houses for sick and well consumptives, and waste of effort.

THE RELATION OF TUBERCULOSIS OF THE BRONCHIAL GLANDS TO THE DIAGNOSIS AND TREATMENT OF TUBERCULOSIS OF THE LUNGS.

By Mary E. Lapham, M.D.,
HIGHLANDS CAMP SANATORIUM, HIGHLANDS, NORTH CAROLINA.

It is beginning to seem more than probable that the first chapter in the story of tuberculosis of the lungs is often written in the bronchial glands, and that if this chapter could be discovered and understood as it is being written in the bronchial glands, that we might prevent the writing of the future chapters in the lungs. This is strongly suggested in those cases characterized by the prodromes of tuberculosis which cannot be confirmed by physical examinations of the lungs: the "pretuberculous cases"—what the French have called "tuberculizable"—cases seeking an examination because there is a history of tuberculosis in the family, or a cough, or the syndrome of tuberculous toxemia. It is precisely in these suspicious cases, when we are unable to find any evidence of tuberculosis of the lungs, that we should remember that all these suspicious prodromes may come from the bronchial glands, and that our search for tuberculous processes is only half-made when we stop with the lungs and do not include the bronchial glands.

Cases of tuberculosis of the bronchial glands without physical signs of tuberculosis of the lungs are dangerous, because they may at any time prove fatal by perforating the trachea, bronchi, esophagus, or bloodvessels, by inducing pathological changes in the lungs which furnish favorable conditions for the growth of tubercle bacilli, and by the direct extensions of tuberculous processes in the bronchial glands into the lungs.

The pressure of enlarged tuberculous glands upon the trachea or bronchi may so compress their bloodvessels that engorgements result in rupture with hemoptysis, hemorrhages, or miliary tuberculosis. Hemoptysis and hemorrhages persisting for years in apparently well subjects with no physical signs in the lungs to explain their occurrence have been very puzzling.

Perforation of the trachea and bronchi by caseating glands may cause sudden and progressively severe dyspnea, closely resembling that of diphtheria with cyanosis, unconsciousness, and death. If the obstruction is removed and the patient survives there may be an acute dissemination of tuberculous pneumonic processes throughout the lobe or the entire lung. These sudden manifestations are very apt to occur in apparently well subjects with no suggestions of the approaching danger and no warning until too late.

The pathological changes induced in the lungs by tuberculous bronchial glands are caused by tracheobronchial stenosis and interference with the return circulation of the blood and lymph from the lungs. Pressure upon the trachea and bronchi may force in their walls, narrowing their lumen, causing stenosis. As the chest wall is pulled out this stenosis is relieved, so that the air enters easily enough. As the lung collapses their walls are pushed together again, the stenosis returns, and it is difficult for the air to escape from the lungs. As soon as the interference with the escape of the air causes sufficient accumulation of residual air in the alveoli, expiratory dyspnea develops; as the stenosis increases and the escape of air becomes more difficult, there is the same difficulty and the same consequences that we have in expiratory asthma; if the intra-alveolar distention becomes sufficiently severe the walls of the alveoli will stretch and the terminal areas of the obstructed, occluded bronchi become emphysematous; the larger the bronchus, the greater the terminal areas supplied and the more extensive the emphysema, so that with sufficient obstruction to the trachea or a main bronchus the whole side may become hyperresonant with diminished expansion. If the entering force of the air should be insufficient to force open the lumen of a smaller bronchus, atelectasis of its terminal area results. If the stenosis sufficiently raises the intrabronchial pressure during expiration, the bronchial walls may stretch and cause bronchiectasis, with the characteristic accumulation of purulent fluid not containing tubercle bacilli. The irritation of the bronchi at the point of stenosis, together with the compression of their blood and lymph vessels, causes stasis, with consequent serous effusions, wet rales, and typical bronchitic and pneumonic conditions. Tuberculosis of the bronchial glands may, therefore, cause tracheobronchial stenosis, with consequent asthmatic, emphysematous, atelectatic, bronchiectatic, bronchitic, and pneumonic conditions in the lungs, which are highly favorable to the growth of tubercle bacilli and the development of tuberculous processes. These conditions are dangerous in themselves, but also dangerous because they are constantly mistaken for primary clinical entities, and the physician is satisfied with the diagnosis of asthma or bronchitis or emphysema, and does not look for tuberculosis of the bronchial glands or lungs. The negative sputum adds to the danger, because it seems to contraindicate tuberculosis.

According to Grancher, the alveolar network of bloodvessels in the lungs holds two liters of blood, and if spread out would cover 150 square meters of surface. Kraemer says: "We have only to remember that all the lymph and blood content of this immense network must pass through the relatively narrow portal of the hilum to realize that slight pressure there might produce enough obstruction to retard the return flow throughout the region of the lung nearest the hilum. Just as enlarged inguinal glands cause edema of the lower extremities and external genitalia, and just as tuberculosis of the cervical glands causes facial edema, so does pressure from enlarged glands within the thorax manifest itself by dilatation of the veins of the face or across the chest or by injuring the recurrent laryngeal, vagus, phrenic, and sympathetic nerves." Just as the mechanical effects of tracheobronchial stenosis predispose to tuberculosis of the lungs by obstructing the escape of air, so the mechanical effects of enlarged glands at the hilum predispose to tuberculosis of the lung by stasis of the lymph and blood currents which is most marked in the region near the hilum, not merely because this region is nearest to the obstruction, but also because the driving force of the collapse of the lung is least felt there. According to von Muralt the force of the collapse of the lung is greatest at the periphery; the greater the distance from the hilum, the greater the force of the circulation; the nearer the hilum, the greater the tendency to sedimentation and depositing out of tubercle bacilli.

The stasis and slowing of the circulation in the regions of the lung near the hilum predispose to the establishing of tuberculous processes there and make the root of the lung the logical site for the beginning of tuberculous processes in the lung. All cases of tuberculosis of the bronchial glands around the hilum threaten the integrity of the lung. These glands at the hilum are in immediate contact with the lung, and, as Osler says: "It is sometimes difficult to determine in a section through the affected lung where the caseous glands terminate and where the lung tissue begins." Bythell insists that in children pulmonary tuberculosis invariably begins at the roots of the lungs. Quoting Bythell, Leslie says: "Out of 330 successive cases of children examined clinically and radiologically he had never seen a single case in which the disease had not obviously originated at the hilus of the lung, nor met one in which the sole or even the primary lesion had been at the apex. Whenever there had been an apical lesion there was in every case revealed by the roentgen-ray a far more advanced lesion at the root of the lung, which had escaped detection by physical examinations, but which was clearly indicated by definite mottling and nodules in the region of the hilus." Bythell regards the glands at the hilum as the actual danger spots and the direct or indirect cause of pulmonary tuberculosis in many cases. Jordan, Cole, Leslie and many others are gradually teaching us that tuberculosis of the apex is secondary to that of the hilum, and has been thought primary because the manifestations are more easily detected there, and also because the apex represents the terminal area of the path through the paravertebral region which tuberculous processes are most apt to follow.

The glands of the hilum are in immediate contact with the lung and the direct extension of tuberculous processes from them into the lung is favored by the associated stasis. The consequences depend upon whether the invaded lung is normal or has been modified by tracheobronchial stenosis. The peribronchitic infiltration of a normal lung has been well described by Jordan. This extension occurs by addition, by aggregation, by sedimentation in the sluggish circulation of the peribronchial tissues of what are more like foreign bodies than aggressive agents; as the tubercle bacilli are deposited out they are encapsulated by connective tissue, there is little or no irritation or hyperemia, the processes are dry, with no exudation; no disintegration of tubercle bacilli, consequently no liberation or absorption of toxins and no syndrome of toxemia. These extensions running along the larger bronchi are purely interstitial and do not affect the mucosa; there is no irritation, consequently no cough, no alteration of breath sounds, and the air content is normal. As the processes reach the smaller bronchi the thickening causes pressure, which may affect the entrance of air into the lumina not well protected by rigid structures, so that suppressed breath sounds over the terminal area of these bronchioles are produced. As soon as the processes reach walls not sufficiently rigid to resist the infiltrations, pressure effects occur. The pathological consequences of peribronchitic infiltrations are not manifested until they reach structures they affect by pressure, and then pain from irritated nerves, collapse of unsupported walls, and atelectatic areas furnish the typical dulness, suppressed breath sounds and the retraction characteristic of fibroid phthisis. This is the gradual fibrosis of the lungs which is not revealed by physical signs until terminal areas are affected. This is the type in which the verdict, "No physical signs in the lungs," therefore no tuberculosis, is so often rendered with such disastrous consequences. Jordan says this is the method of extension in 50 per cent. of all cases of tuberculosis of the lungs, and that physical signs are not and cannot be present until the terminal areas are reached. This type is dangerous, not only because it may of itself cause death, but also because a multitude of factors may at any time change dry into wet processes, with consequent caseation and softening.

When tuberculous processes extend into a lung which is not normal, but which has been modified by tracheobronchial stenosis or pressure around the hilum, the consequences will depend upon the chief results of the modifications. In one case it may be bronchitic or asthmatic or emphysematous conditions; in another atelectasis. There may be as many different results in the lungs as there are modifying factors producing these results. Wherever the tissues are wet, the foundations for caseous broncholobular pneumonias exist. Wet areas mean caseation with disintegration of lung tissues and tubercle bacilli, the liberation and absorption of toxins, and the syndrome of toxemia.

It has often been asserted that broncholobular pneumonias represent the origin of tuberculous processes in the lungs. That tubercle bacilli are carried to the alveoli by inspiration, and in the alveoli develop and extend from one infundibulum to another until the whole lobule is involved. This racemose or acinous infiltration of lobules is commonly regarded as the type of origin, but it is possible that in some cases the reverse is true, and that extension occurs from the bronchial glands along the peribronchial sheaths to the alveoli, thus causing a lobular infiltration because the lobule is the terminal area of the bronchus. Lobular bronchopneumonias would be the logical result of peribronchial infiltrations into edematous tissues.

The relation of tuberculosis of the bronchial glands to the diagnosis of that of the lungs consists in the recognition of cause and effects. The entrance into and escape from the lungs of air, lymph, and blood are interfered with by the pressure of enlarged bronchial glands upon the air, lymph, and blood-passages. If the lung is dry the effect is chiefly upon the air passages, and we find that not enough air is entering the alveoli to expand them promptly and uniformly. We can hear the slow, uneven, delayed, insufficient expansion of the alveoli, and we know that either there is obstruction to the sufficient entrance of air or that the lobules are tied down in some way so as to restrict their expansion. If the obstruction more especially concerns the escape of air from the lungs then the delayed collapse of the alveoli and prolonged expiration suggest tracheobronchial stenosis. If the pressure upon the air passages is sufficiently great, the breath sounds are more or less suppressed and are louder after coughing when an extra volume of air is forced in. In peribronchitic infiltrations the character of the breath sounds is not so much changed as their volume. Harshness and granular breathing do not appear until there is roughening of the mucosa. The typical changes in the gradual fibrosis of the lung concern the interstitial tissues chiefly and do not cause dulness until atelectasis develops. Suppression of breath sounds and insufficient, irregular expansion of the alveoli are the landmarks of peribronchitic infiltrations as they thread their way through a dry lung. Pain in the terminal areas is often characteristic, and is probably caused by pressure upon the accompanying nerves.

When the return circulation of blood and lymph from the lung is obstructed and the lung is subjected to the backward pressure and danger of edematous infiltrations, the physical signs are those of wet conditions. It is much easier to detect these evident changes, and they are much more pronounced, but they are sometimes mistaken for other conditions. Chronic bronchitis, asthma, and emphysema often cloak tuberculous processes, and acute infections for a time often reveal them; but as the acute hyperemia disappears and the wet sounds dry up we fail to see the connection between existing peribronchitic infiltrations and transient physical signs. We ascribe to grippe, typhoid, measles, and colds the power to initiate tuberculous processes in the lung, but it is possible that they reveal the existence of these processes.

The treatment of tuberculosis of the lungs is influenced by the knowledge that there is an etiological relationship with that of the bronchial glands, because these glands must first be healed before the chancre of perpetual reinfection is removed. This emphasizes the necessity for time. Long after the physical signs in the lungs have become favorable, just as it was long before they were manifested, the sore spots in the bronchial glands remain dangerous and difficult to control. It is possible that the persistency of these sources of infection explains the relapses and the failures to maintain recovery in many cases. The diagnosis and treatment of tuberculosis of the lungs may begin and end in that of the bronchial glands.

A CASE OF DIABETES INSIPIDUS WITH A PECULIAR NECROPSY FINDING IN THE POSTERIOR LOBE OF THE PITUITARY BODY.

By F. Parkes Weber, M.D., F.R.C.P.,
SENIOR PHYSICIAN TO THE GERMAN HOSPITAL, LONDON,
AND
Hans Schmidt, M.D.,
RESIDENT MEDICAL OFFICER TO THE HOSPITAL.

Various changes have been described in the pituitary gland and its neighborhood, at the base of the brain, as having been discovered at postmortem examinations on cases of diabetes insipidus.

J. Camus and G. Roussy[1] are among those who have experimented on the subject. About eighteen dogs were operated on and various areas at the base of the brain in the immediate neighborhood of the pituitary gland were destroyed, and in some animals the pituitary gland itself was destroyed. By these experiments it was proved that polyuria may result even when the lesion is not limited to the pituitary gland. In five cases polyuria resulted, though the experimental puncture did not touch the pituitary gland. The infundibulum seems to be of special importance, and one observation showed that if the infundibulum were preserved it was possible for the pituitary gland itself to be removed without polyuria resulting.

By some authors the "pars intermedia" of the pituitary body has been specially incriminated.[2] Ependymitis, or tumor of the floor of the fourth ventricle, has occasionally been accompanied by diabetes insipidus,[3] and Claude Bernard, as is well known, was able to experimentally produce simple polyuria in animals by puncture of the floor of the fourth ventricle at a point a little above his so-called "glycosuric centre."

The relations between the pituitary gland and diabetes insipidus have recently been dealt with by C. Römer,[4] M. Simmonds,[5] Harvey Cushing,[6] P. Fleurot,[7] D. B. Jewett,[8] Erich Meyer[9] and others; and the allied subject of the effect of metastatic tumors of the pituitary gland has been discussed by Simmonds[10] and S. Erdheim,[11] the latter demonstrating the case of a woman with "Simmonds's syndrome" (the association of mammary carcinoma with polyuria, due to cancerous metastasis in the pituitary gland). Many papers have also been published more or less bearing on the relations of the pituitary gland to imperfect sexual development and infantilism as well as to diabetes insipidus.[12]

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[1] Comptes rendus de la Société de biologie, Paris, 1914, lxxvi, 773 and 877; see also Camus and Roussy, Diabète Insipide et Polyurie dite Hypophysaire, Presse médicale, Paris, 1914, xxiii, 517.

[2] Cf. E. Frank, Ueber Beziehungen der Hypophyse zum Diabetes insipidus, Berl. klin. Wchnschr., 1912, xlix, 393.

[3] K. Pichler, Zentralbl. f. inn. Med., Leipzig, 1903, xxiv, 745. Pichler gives references to similar cases in the literature. Cf. the old experiments of Claude Bernard on the Experimental Production in Animals of Glycosuria and Simple Polyuria.

[4] Deutsch. med. Wchnschr., 1914, xl, 108; and C. Römer, München. med. Wchnschr., 1913, lx, 2755 (Aerztlicher Verein in Hamburg, November 25, 1913).

[5] München. med. Wchnschr., 1913, lx, 127.

[6] The Pituitary Body and its Disorders, 1912, pp. 17, 267.

[7] Thèse de Doctorat, Paris, 1914.

[8] Med. Record, New York, 1914, lxxxv, 242.

[9] Berl. klin. Wchnschr., 1912, xlix, 1642 (unterelsässicher Aerztev., June 29, 1912).

[10] München. med. Wchnschr., 1914, lxi, 180.

[11] K. k. Gesellschaft der Aertze in Wien, May 29, 1914, Wien. klin. Wchnschr., 1914, xxvii, 867.

[12] See Erich Ebstein, Ueber Eunuchoidismus bei Diabetes insipidus (with many references to previous literature), Mitt. a. d. Greuzgeb. d. Med. u. Chir., 1913, xxv, 441. A. von Strümpell, Med. Gesellsch. zu Leipzig, January 20, 1914; München. med. Wchnschr., 1914, lxi, 504. Pierre Marie and Boutier, Société de Neurologie, Paris, April 3, 1913 (Rev. neurol., Paris, 1913, xxi, 555); F. P. Weber, Brit. Jour. Child. Dis., 1912, ix, 211; T. R. Whipham, Proc. Roy. Soc. Med. (London), Section for Diseases of Children, 1915, viii, 10; Sprinzels, Wien. klin. Wchnschr., 1912, xxv, 937 (K. k. Gesellsch. der Aerzte in Wien, June 7, 1912).

In many cases of diabetes insipidus, symptoms have been observed during life pointing to the presence of lesions at the base of the brain. Clinically a connection between diabetes insipidus and congenital or acquired syphilis has often been suspected; in some cases the belief in such a connection has, I think, received confirmation *ex juvantibus*, that is to say, from satisfactory results of antisyphilitic treatment. In several other cases a connection of some kind with tuberculosis seems to have existed.

Our present case is that of a tuberculous man who suddenly developed diabetes insipidus about two years before his death, which was due to pulmonary and laryngeal tuberculosis. At the necropsy a peculiar change in the posterior lobe of the pituitary body was found.

Case History. The patient, F. A., aged thirty-seven years, was admitted to the hospital on March 31, 1915, and died on June 21. He was a thin man, weighing 115 English pounds on admission, and said he had lost nine pounds in weight during the previous nineteen days. His polyuria had apparently commenced suddenly in August, 1913, after a slight operation on his neck, probably the removal of an enlarged lymphatic gland from the right side. This operation did not prevent him making a long railway journey on the same evening, but he commenced to experience great thirst (polydipsia) immediately afterward, and since then he had continuously suffered from polydipsia and polyuria. During the last two months he had had a cough and anorexia, and for one month he had been expectorating mucopurulent sputum.

In the hospital he presented the physical signs of pulmonary and laryngeal tuberculosis, had a hectic type of fever, and steadily lost ground. His mucopurulent sputum swarmed with tubercle bacilli. His urine, which was of about the same specific gravity as ordinary tap-water, pale, clear, and free from albumin and sugar, averaged about 10 liters in the twenty-four hours, sometimes more, sometimes less. On one occasion the daily quantity was as much as 13,250 c.c. His blood serum gave a negative Wassermann reaction for syphilis. His brachial systolic blood-pressure varied between 90 and 115 mm. Hg. His pupils were equal and reacted properly to light and accommodation. Ophthalmoscopic examination showed nothing abnormal. There was no hemianopsia; the visual fields (both for white and for colors) and visual acuity were normal (Dr. C. Markus). Roentgen-ray photographs of the base of the patient's skull (taken by Dr. James Metcalfe) seemed to show that there was no enlargement of the pituitary fossa. During the last days before the patient's death (June 21, 1915) the average amount of urine was less, namely, about 6000 c.c. in the twenty-four hours.

Necropsy and Microscopic Examination. Both lungs were "stuffed with" miliary tubercles; there were no cavities. There was tuberculous laryngitis (macroscopic and microscopic examination). The heart, pericardium, and aorta showed nothing special. The liver was not enlarged, but looked somewhat fatty. The spleen was slightly enlarged, measuring 12 x 8 x 4 cm., but otherwise by macroscopic and microscopic examination it appeared normal. The kidneys, suprarenal glands, and thyroid glands likewise appeared normal (microscopic as well as macroscopic examination). Nothing special was observed in the pancreas, alimentary canal, or in the testis or epididymis on either side. There were some enlarged lymphatic glands in the neck. The bone marrow of the head and upper part of the shaft of the left humerus was examined macroscopically and looked as if it had not undergone much hemopoietic reaction. The spinal cord was not examined, and in the examination of the brain nothing abnormal was observed excepting with regard to the pituitary body.

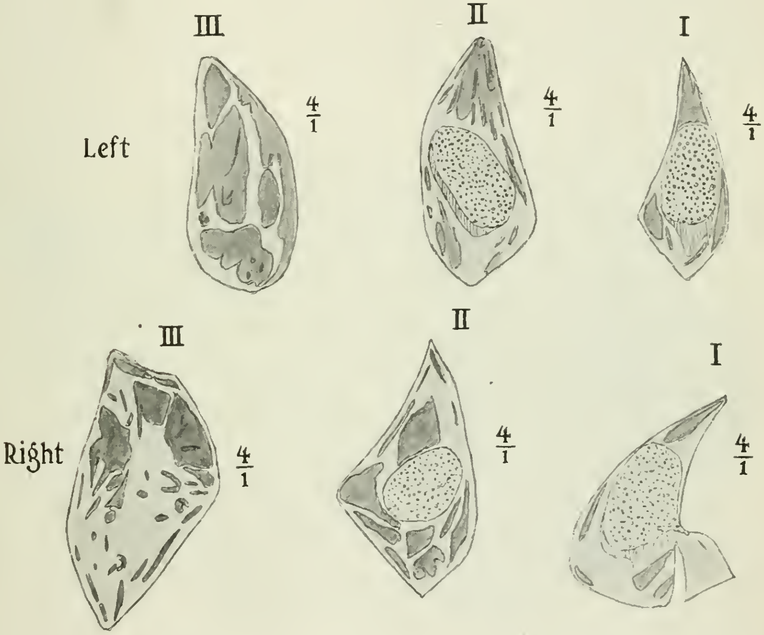

Fig. 1.—A series of six sections of the pituitary body cut parallel to each other, on a vertical-sagittal plane. They are represented diagrammatically four times their natural size. The three in the upper row were cut to the left of the middle line and the three in the lower row were cut to the right of the middle line. The pair marked *I* are those nearest the middle line; the pair marked *III* are those farthest from the middle line; while the pair marked *II* were cut on a plane between *I* and *II*. In these sections the dotted portions represent the anterior lobe (pars glandularis), while the rest represents the posterior lobe (pars nervosa). The two lateral sections (*III*) consist exclusively of posterior lobe substance, while in *I* and *II* the anterior lobe substance is almost completely surrounded by posterior lobe substance. The dark portions in the posterior lobe substance are areas of the yellowish-brownish lipoid cells. (See Figs. 2 and 3.)

The Pituitary Body. At the necropsy the pituitary fossa was found to be not much if at all enlarged, but the posterior lobe of the pituitary body appeared abnormal, and the whole region was removed for further examination. Several sections of the pituitary body were cut; all of them were cut parallel to each other, on a vertical sagittal plane. There could be no doubt whatever that the posterior lobe (pars nervosa) was relatively enlarged in proportion to the anterior lobe (pars glandularis). The posterior lobe almost completely enclosed the anterior lobe, and was of a yellowish-brownish color, the color appearing to spread right into the posterior wall of the pituitary fossa. Fig. 1 represents diagrammatically six of the sections under low magnification (four times the natural size). The three in the upper row were cut to the left of the middle line and the three in the lower row were cut to the right of the middle line. The pair marked *I* are those nearest (to the left and right respectively of) the middle line. The pair marked *III* are those farthest from the middle line, while the pair marked *II* were cut on a plane between *I* and *III*. In these sections the dotted portions represent the anterior lobe (pars glandularis) while the rest represents the posterior lobe (pars nervosa), which in *I* and *II* is seen to almost completely surround the anterior lobe. The two lateral sections (*III*) consist exclusively of posterior lobe substance. The dark portions in the posterior lobe are areas of the yellowish-brownish substance which has given the posterior lobe its decided color.

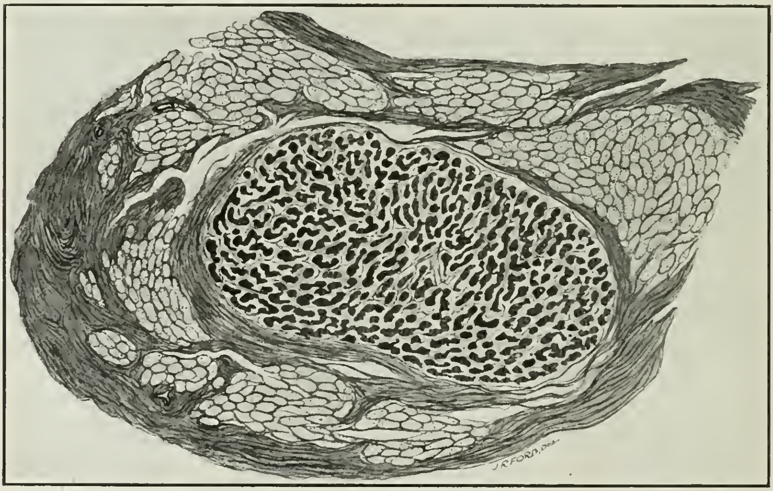

Fig. 2.—A drawing of a section of the pituitary body (magnified 15 times) similar to *II* in the lower row of Fig. 1. The substance of the anterior lobe, which has the normal glandular structure, is almost completely surrounded by posterior lobe substance, which is remarkable for containing large clumps of granular cells.

Fig. 2 is a drawing of a section similar to *II* in the lower row of

Fig. 1, but under considerably higher magnification (magnified 15 times). The substance of the anterior lobe is seen to present the normal glandular structure, but the posterior lobe, which almost completely surrounds it, is remarkable for containing large clumps of granular cells. Part of one of these clumps (from a section stained with Sudan III), magnified 300 times, is represented in Fig. 3, so as to further illustrate the nature of the cells in question. They are rather large cells with small nuclei, which stain deeply with hematoxylin. Their cytoplasm has a granular appearance and many of them take on the Sudan III coloration very well, and show that the granules are really minute droplets of a lipoid substance. In others of these cells, which stain less well with Sudan III, the cytoplasm appears to be full of minute crystals, doubtless fatty acid crystals of some kind; and probably it was a transformation of the lipoid droplets into fatty acid crystals that caused these cells to take on the Sudan III stain relatively badly.

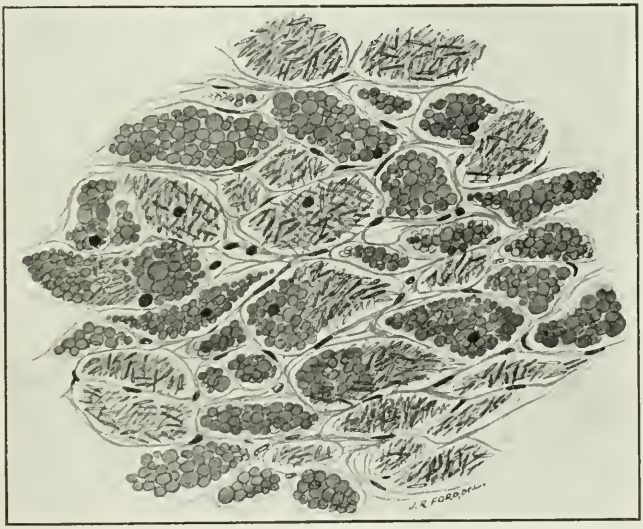

Fig. 3.—A drawing from one of the clumps (see Fig. 2) of cells in the posterior lobe substance of the pituitary body (magnified 300 times). The cytoplasm of some of these cells is full of minute lipoid droplets which have taken on the Sudan III stain very well. The cytoplasm of others of the cells is rich in fatty acid crystals and has taken on the Sudan III stain relatively badly.

We think that these cells, which are possibly of neuroglial origin, may be regarded as one kind of "compound granular cells" (Körnchenzellen), the presence of which in considerable numbers forms a feature in various abnormal conditions of the central nervous system. Doubtless the lipoid-containing cells in question gave the posterior lobe substance of the pituitary body in the present case its decided yellowish-brownish pigmentation, which reminded one of the color of the cortex of suprarenal glands and of some tumors of suprarenal cortical origin.

Many changes in the pituitary body and the base of the brain have (as we pointed out at the commencement of this paper) been described in cases of diabetes insipidus, but we are not aware that an exactly similar change to the one observed in our present case has as yet been recorded. It is impossible to avoid the conclusion that the changes in the pituitary body in the present case were in some way the result of the patient's tuberculosis.

In conclusion, we have to thank Mr. S. G. Shattock, Dr. J. C. G. Ledingham, and Dr. Kinnier Wilson for very kindly helping us in the examination of the sections.

Note.—In producing the three figures the original drawings have been considerably reduced, Figs. 2 and 3 by one-quarter and Fig. 1 by two-fifths. The printed descriptions are therefore no longer correct in regard to the question of magnification.

REVIEWS

FRACTURES AND DISLOCATIONS. By KELLOGG SPEED, S.B., M.D., F.A.C.S., Associate in Surgery, Northwestern University Medical School; Associate Surgeon, Mercy Hospital; Attending Surgeon, Cook County Hospital, Chicago, Ill. Pp. 888; 656 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

IN the preparation of his book the author has used material from his own experience and culled other information from the literature on the subject. He contends, and wisely, that intelligent treatment of fractures and dislocations must be based on a proper conception of the pathology involved. A clear conception of the nature of the bony injury in fractures is essential and this can be had only with the aid of sufficiently numerous roentgen-ray views. These views the author has interpreted in his book by making careful line drawings of the fractures, thus obviating the possible misinterpretation so common in the reading of a fracture plate. He does not, however, lay enough stress upon the necessity of having two views of every fracture. Such illustrations are noticeably lacking especially in the fractures of the upper half of the femur. It is well known that an anteroposterior view shows frequently good position when a lateral view will show no approximation at all.

The chapter on the operative treatment of fractures is very interesting, instructive and up to date. The author here states that bone work is best done by experienced surgeons in this line and that strict asepsis must be observed. Perfectly true, but such surgeons are made by experience which, unfortunately, must be gained.

The use of the Steinmann nail extension is spoken of and advocated as the best in many fractures needing extension. The writer should, however, describe the removal of a modern Steinmann nail which unscrews in its middle thus allowing half to be pulled out each side and not necessitating pulling an exposed, supposedly dirty end through the tissues and bone.

The treatment by external fixation is well and thoroughly described but could be improved by more detail as regard the dressings and splints. More illustrations of the completed final dressing would be a great addition, for in reality after the reduction this is the important feature in all fracture treatment. There are many splints, plaster moulds and methods of fixation and traction generally unknown that could well be incorporated in this excellent work, preferably presented as illustrations.

The book is thoroughly well written and edited and is unusually free from typographical errors. It covers the subject completely and is a treatise that any physician or surgeon should have at his command. E. L. E.

VENEREAL DISEASES. A MANUAL FOR STUDENTS AND PRACTITIONERS. By JAMES R. HAYDEN, M.D., F.A.C.S., Professor of Urology in the College of Physicians and Surgeons, Columbia University, New York. Fourth edition. Pp. 365; 133 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

THE fact that this work of Hayden's on venereal diseases has already passed through three editions is sufficient testimonial as to its merit and popularity. This new edition has been thoroughly revised and enlarged and the subject matter brought up to date with the addition of numerous new illustrations.

Dr. Hayden has covered the subject in a notably clear and concise manner, and it is obvious that his presentation is the expression of personal experience. Of the thirty-six chapters, eighteen are devoted to syphilis, nine to gonorrhea, and nine to other forms of venereal disease.

It occurs to the critic that insufficient and disproportionate space is given to seminal vesiculitis as compared with prostatitis; also that the author is incredulous of the value of epididymotomy, at least that the indications and contra-indications are not satisfactorily drawn.

Many will disagree with Hayden relative to the treatment of acute posterior urethritis by injections and irrigations by using a catheter. Again, in view of the generally acknowledged utility of sera and bacterins especially in gonorrheal arthritis, more stress might be laid on therapy by these agents, including a statement of the technic of their administration.

We do not agree that excision of the chancre, when practicable, is of no value, and that so soon as the initial lesion of syphilis appears the entire system is infected to maximum degree. Contrary to the majority opinion, the author apparently places mercury as the sheet anchor in the treatment of syphilis, as the description of its administration precedes that of salvarsan or neosalvarsan. We would also take exception to the statement that it is "not worth while to test the complement fixation reaction until after the end of the second year" of antisyphilitic treatment.

Considered in its entirety, this book is most admirable, and is the most practical treatise on venereal diseases extant for the use and guidance of general practitioners and students. B. A. T.

A Text-book of Practical Gynecology. By D. Tod Gilliam, M.D., Emeritus Professor of Gynecology in Ohio State University College of Medicine, and Earl M. Gilliam, M.D., Professor of Diseases of Women in the Ohio State University. Fifth revised edition. Pp. 681; 366 illustrations. Philadelphia: F. A. Davis Company, 1916.

The mere fact that this book is now in its fifth edition should be *prima facie* evidence that it has merits and is extensively used. There are one or two features of the book, however, which must bear criticism. It is surprising to note, in spite of the fact that the book is just off the press, that the subject of radium and roentgen-therapy is not even mentioned. The general arrangement of the book shows carelessness, as for example the interposition of a chapter on upper abdominal surgery between two chapters on ovarian conditions. The illustrations might have answered for the first edition of this work, but we certainly expect something better than crude drawings at this late date. The chapter on the urinary organs is antiquated and is badly in need of revision. In short, this text-book in its present state, cannot be favorably compared with the more recent contributions to the subject. F. E. K.

Manual of Otology. By Charles Edwin Perkins, M.D., F.A.C.S., Professor of Clinical Otology in New York University and Bellevue Hospital Medical College. Pp. 445; 120 engravings. Philadelphia and New York: Lea & Febiger, 1916.

For a text-book for students and practitioners, as this *Manual* professes to be, it is one of the most concise, lucid, and thorough that the reviewer has seen, and it might with propriety and profit be studied by the fairly advanced specialist as well, as it gives accurate scientific information concerning all of the more common, and most of the rare diseases of the ear. Especially to be commended, from the stand-point of the student, are the early chapters on anatomy, physiology, and methods of examination, in which the subjects are treated in a manner different from the somewhat stereotyped form of most manuals, and with an originality in text and illustration that makes an intricate study both clear and interesting. While the work shows largely the results of the author's personal experience, there is a commendable absence of case histories, which have always seemed to the reviewer to be out of place in a work of limited size and scope.

One of the most interesting and instructive features of the book, perhaps, is the space devoted to diseases of the internal ear, particularly of the vestibular portion, for, through the recent researches of well-known workers, the part this organ plays in modern medical diagnosis is rapidly becoming prominent, and it is a necessity for anyone professing to do ear work to at least understand the fundamental laws governing the spontaneous and induced vestibular reactions, their relations to other parts of the body, and their value in differential diagnosis. Very wisely, however, the author has not gone into the fascinating realm of cerebellar localization, which abstruse subject is eminently out of place in a work of this character.

Dr. Perkins' descriptions and illustrations of operative procedures are all that could be desired, and the reader is not burdened with several different methods of operating, where one standardized one will suffice.

Many of the excellent illustrations with which the book abounds are from photographs; others are well planned schematic representations, and the accompanying explanatory text is very clear. All are original. Altogether it is a complete and practical text-book, full of interest and instruction for anyone. G. M. C.

Care and Feeding of Infants and Children. By Walter Reeve Ramsey, M.D., Associate Professor of Diseases of Children, University of Minnesota. Pp. 290; 123 illustrations. Philadelphia: J. B. Lippincott Company, 1916.

This book is written for nurses. A nurse who studied and retained the information contained between its covers would not only be better informed than most of her profession, but would be quite sure to know more about babies and children than most physicians. In other words the book is well written and thorough. The chapters are logically arranged, and good judgment is used in not making certain ones too intricate. The illustrations convey what they should very clearly, and are well selected. A. G. M.

Medical and Surgical Reports of the Episcopal Hospital. Edited by Astley P. C. Ashhurst, M.D. Volume III. Pp. 352; 126 illustrations. Philadelphia: Wm. J. Dornan, 1915.

The third volume of the *Reports of the Medical and Surgical Staff of the Episcopal Hospital* is a splendidly constructed and admirably edited example of what a hospital report should be. A hospital report of this type is meant primarily to put on record the work that is done in the hospital and to report cases of an unusual type which are worthy of record, but which, for various reasons, would not be placed in current medical periodicals. This is what has been accomplished in the present volume. Methods of diagnosis and results of treatment as practised in the Episcopal Hospital are reported as well as numerous unusual cases. The great majority of these would probably not see the light of cold print were it not for the hospital report, and thereby there would be a loss to the medical world.

The editor of this volume is certainly deserving of much praise. Probably without his energetic efforts it would have been impossible to have secured so many admirable contributions; it is certainly through his efforts that such a first-class and complete publication has been achieved. J. H. M., Jr.

THE BASIS OF SYMPTOMS. THE PRINCIPLES OF CLINICAL PATHOLOGY. By Dr. LUDOLPH KREHL, Ordinary Professor and Director of the Medical Clinic in Heidelberg. Translated from the seventh German edition by A. F. BEIFELD, Instructor in Medicine, Northwestern Medical School, with an introduction by A. W. HEWLETT, Professor of Internal Medicine, University of Michigan, Ann Arbor. Pp. 517. Philadelphia and London: J. B. Lippincott Company.

AFTER an interval of nine years, Hewlett's well-known translation of Krehl's *Clinical Pathology* now appears in a third English translation by Beifeld under the new title of *The Basis of Symptoms*. The translator states that the change was made in order to emphasize the immediate relation of the contents to clinical medicine. Nevertheless, in view of the popularity of the former editions and the close adherence of the present to the former texts, the advantage of such a change of titles is at least questionable. In other particulars, however, the translator's service is excellent. In many instances his parenthetical additions alone save the treatment of a given topic from being inadequate and antiquated, and it is only a pity that more care was not observed in placing the German text in better harmony with the translator's more modern view-point. Examples of such valuable inserts can be found in the discussions on the origin of the heart beat (pages 53 and 54), paroxysmal tachycardia (pages 57 and 58), auricular fibrillation (pages 65 and 66), Fischer's theory of edema (page 93), the cytodiagnosis of exudates (page 94), the relation of the hypophysis to adiposity (page 318).

The twelve chapters treat of (1) the circulation; (2) the blood; (3) infection and immunity; (4) respiration; (5) digestion; (6) nutrition and metabolism; (7) disturbances of carbohydrate mechanism; (8) metabolism of the purin bodies; (9) constitutional diseases and diatheses; (10) fever; (11) secretion of urine; (12) nervous system. One regrets the absence of discussion of such topics as auricular flutter, venous blood-pressure, blood-platelets in hemorrhagic diseases, acidosis factors in dyspnea and kindred subjects. The references which were formerly at the bottom of each page have been much extended and collected at the end of each chapter. The great preponderance of German citations to the neglect of English-speaking authorities is unfortunate, though hardly unexpected. A case in point is found in the relationship of the islands of Langerhans to diabetes, where Weichselbaum is quoted and Opie's work omitted. The illustrations of the former editions have been removed, so that this edition only contains twelve more pages than does the second.

As the earlier editions of this book do not appear to have been reviewed in this JOURNAL, a few remarks on the nature of the work will perhaps not be considered out of place. As both of its English titles imply, it is an attempt to "interpret the various pictures observed in the clinic from the stand-point of disturbed physiology" and "to foster a more definite leaning (by the clinician) upon the biological sciences in general." Perusal of any one of the twelve chapters will undeniably foster these admirable principles; but it is also true that the various branches of this important and far-reaching subject can in 520 pages necessarily only be touched upon in a cursory if not superficial manner. He would, indeed, be doomed to disappointment who felt that after reading the chapter on the circulation, for instance, he had really covered all the disturbances in function of this extensive system. As a text-book, then, of an important branch of medicine, or as a valuable repository of pathologico-physiological facts, the book leaves much to be desired; as a correlation of a certain number of clinical symptoms with their pathological causes and as a stimulus to the "functional outlook on disease," it should be a valuable reminder to many practitioners and a pleasant review to a still wider circle. E. B. K.

DISEASES OF OCCUPATION AND VOCATIONAL HYGIENE. Edited by GEORGE M. KOBER, M.D., LL.D., Professor of Hygiene, Georgetown University, Washington, D. C.; President of the Section on Hygiene of Occupations, XV International Congress on Hygiene and Demography; Chairman of the Section on Industrial Hygiene of the American Public Health Association (1915); Secretary of the Association of American Physicians, and WILLIAM C. HANSON, M.D., formerly with the Massachusetts State Board of Health. Pp. 918; 42 figures. Philadelphia: P. Blakiston's Son & Co., 1916.

IT was inevitable, in view of the recent awakening in this country to the importance of vocational diseases and hygiene, that a comprehensive text-book upon the subject should appear. Until very recently, however, this has been impossible on account of the paucity of American statistical data. The publications of the *Transactions of the XV International Congress on Hygiene and Demography,* of the latest mortality statistics by the United States Census Bureau, and of industrial insurance statistics by the Metropolitan Insurance Company as well as of numerous monographs upon special investigations have greatly improved this situation. Consequently, it has been possible for Kober and Hanson to give us in this volume the most complete and authoritative presentation of the subject yet submitted to the English-speaking public.

It is really three books in one. The first one, designated Part I, is in itself a system of the diseases of occupation. The occupational intoxications are discussed by such authorities as Thomas M. Legge, Emery R. Hayhurst, George L. Apfelbach, Sir Thomas Oliver, Harry Linenthal, Alice Hamilton, Louis Casamajor, and Ludwig Teleky, *privat dozent* for social medicine at the University of Vienna. Anthrax and the relation of parasites to occupation are described by Langdon Frothingham and Bailey K. Ashford respectively. Compressed-air illness is presented by Seward Erdman, whose name is identified with the investigation of those cases which occurred during the construction of the East River tunnels in New York. The final one of the specific occupational diseases, that of diminished atmosphere, especially as seen in aviators, is most interestingly presented by the senior editor.

The systemic occupational diseases, including the dust diseases of the lungs and diseases of the blood, circulatory system, and kidneys are covered by Sir Thomas Oliver and Thomas S. Lee. One of the most scientific and valuable chapters in the entire volume is that upon fatigue and occupation, by Fredric S. Lee, who is the recognized leader in this line of research in this country. Chapters upon occupational affections of the nose, mouth, throat, eye, ear, and skin are presented by specialists in the particular fields of study. Oliver closes this section of the book with a discussion of electrical injuries and electrical shock.

Part II, 347 pages, deals with the etiology and prophylaxis of occupational diseases in general and with vocational hygiene as related to the processes which are injurious to health. It is contributed almost entirely by Dr. Kober, and will be of interest to employers, employees, public health officials, and indeed all those interested in the prevention of occupational hazards. There is also included in this part of the book the list of industrial poisons which was edited by the permanent advisory council of hygiene of the International Association for Labor Legislation. It covers 54 poisons, giving for each the branches of industry in which the poisoning occurs, the mode of entrance into the body, and the symptoms of poisoning. There are other valuable tables in this section.

Part III has to do with the relation of clinics, statistics, govern-mental study, and legislation to occupational diseases. Among its most interesting chapters are those of Luigi Devoto, professor and director of the Milan Clinic, the first clinic established for occupational diseases, upon the purposes and accomplishments of that clinic, and of Frederic L. Hoffman upon the mortality from tuberculosis in dusty trades. A chapter by George C. Whipple, of the Massachusetts Institute of Technology, upon the uses and fallacies of statistics will be appreciated by all who are not familiar with the technical difficulties of statistical data. This part of the book is planned to be of special help to those called upon to investigate the relations of occupation to disease. T. G. M.

MEDICAL CLINICS OF CHICAGO. Vol. II, Nos. 1 and 2. Philadelphia and London: W. B. Saunders Company, 1916.

The Medical Clinics of Chicago have now completed their first year of active publication and are starting out on the second, apparently with no decrease in vigor and considerable improvement in general character. The first number of the new volume contains several important and interesting clinics, and likewise one or two which might have well been omitted. Comparisons are odious, but it would be unfair not to mention certain contributions in this number: Dr. Brophy gives a splendid medicodental discussion on Oral Infection, Dr. Abt discusses most completely the Feeding of the Normal Baby, and Dr. Edwards gives a well-prepared lecture on the Use of Digitalis.

The second number of the second volume is likewise interesting and instructive. Dr. Portis has a very interesting but rather incomplete clinic on Syphilis of the Stomach. Dr. Abt's article can be again selected for special commendation, as well as that of Dr. Biefeld.

Taking everything into consideration it can be said that the clinics are showing a healthy improvement, but there are still criticisms which may be made and which have been made, and which still hold good, but, on the whole, they present a novel method of giving to a larger class of physicians a most valuable course in clinical medicine. J. H. M., JR.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

The Vaccine Treatment of Asthma, in Bengal.—L. ROGERS (*Practitioner*, 1916, xcvi, 573) reports a series of 13 cases of bronchial asthma treated with autogenous vaccine. Cultures were made on glycerin-agar tubes from freshly obtained sputum, two tubes being inoculated from a single loopful, and about six tubes used in each examination to ensure some of the colonies being well separated. On the following day, subcultures were made from the fine pneumococcal and streptococcal-like colonies, a number of them being taken up so as to get as many strains as possible in the tubes used for making the vaccine. Occasionally the culture consisted so purely of fine colonies that the vaccine could be prepared from the primary culture, but this was exceptional. If the subculture was a thin one, it was smeared over the surface with a platinum loop and reincubated until a uniform thin layer of growth was obtained. Five cubic centimeters of sterile salt solution were added to each tube, which was then heated to from 56° to 60° for one hour; 0.5 per cent. of carbolic acid was added, and after mixing well the fluid was put up in doses of 0.5 and 1 c.c. The first dose was 0.5 c.c., which usually contained about 50,000,000 organisms. If no febrile, but only a slight local reaction occurred, a dose of 1 c.c. was given in five days and repeated weekly. Occasionally it was necessary to increase the dose to 2 c.c. The organisms present varied considerably in different cases, while some of the vaccines were mixed cultures of more than one variety of coccus. Most frequently diplococci were found in the largest numbers and sometimes nearly in pure culture. They were nearly always Gram-positive and sometimes capsulated. Streptococci were also commonly present, and were sometimes the predominating organisms. The cultural characteristics of the organisms were not studied for lack of time. Cures are reported in a number of instances, the largest being of two and a half years' duration. All but two of the patients showed decided benefit, and in these the treatment was discontinued before it could be given a fair trial.

The Etiology of Epidemic Poliomyelitis.—E. C. Rosenow, E. B. Towne and G. W. Wheeler (*Jour. Am. Med. Assn.*, 1916, lxvii, 1202) report results of their recent investigations of epidemic poliomyelitis in a preliminary note. They have made a bacteriological study of throats, tonsils, blood, spinal fluid, the central nervous system, and other tissues in cases of acute poliomyelitis in the present epidemic both in Rochester, Minn., and in New York City, with particular reference to the infecting power of the bacteria isolated. They isolated a peculiar polymorphous streptococcus, often in large numbers, from the throat, from material expressed from tonsils, and from abscesses in tonsils of a large series of cases of epidemic poliomyelitis. They also obtained similar organisms from the ventricular fluid after death and from blood during life in one instance but not from the spinal fluid. In twelve consecutive cases of poliomyelitis which came to autopsy in New York, they obtained this same organism from the brain and cord and from the intervertebral ganglia and lymph nodes in some of the cases. This confirmed the results of Mathers in his studies of the brain and cord. The polymorphous streptococcus produces on aërobic blood-agar plates fine, dry, non-adherent, slightly green colonies which may show a hazy zone of hemolysis after forty-eight hours. The cultural characteristics vary with the conditions of artificial growth employed. Involution forms may occur. One of the striking characteristics of this organism appears to be the fact that with changes in its artificial medium it becomes transformed from a relatively large coccus to an extremely minute organism resembling the globoid bodies described by Flexner and Noguchi. After filtration of cultures through Berkefeld N filters a growth can be obtained from the filtrate, and in suitable medium, the large forms may be obtained from this material which originally contained only the small globoid bodies. Paralysis with lesions in the central nervous system has been produced in guinea-pigs, rabbits, dogs, cats, and monkeys by intravenous or intracerebral injection, with this peculiar streptococcus from practically all of the 52 cases of acute poliomyelitis. Furthermore, it has been produced by injecting the emulsions of pus expressed from tonsils, emulsions of extirpated tonsils and emulsions of the brain. It has also followed injection of the primary mixed culture containing chiefly the peculiar streptococcus, and by injection of the pure cultures from throats, from material expressed from tonsils, and from the abscesses in tonsils removed from living patients and necropsy cases. Similar results have been secured from cultures obtained from the brain and cord.

Lead Poisoning from Projectiles Retained in the Body.—M. Loeper and G. Verpy (*Progrès méd.*, 1916, xl, 81) report studies on 16 patients carrying old lead projectiles embedded in their tissues. The authors had observed symptoms which they found difficult to explain, *i. e.*, hypertension, albuminuria and cylindruria, constipation and colic, and anemia. Suspecting that the patients might be suffering with a latent saturnism, they made chemical examinations of their urines, and in six of the sixteen they demonstrated the presence of lead. The lead was found to the amount of 0.5 to 1 mg. per liter of urine, or an excretion of more than 1 mg. daily. The intestinal and nervous symptoms they could not relieve, but in three cases the albuminuria (0.5, 0.75, and 3 gm. per liter respectively) disappeared completely within two to three weeks after removal of the lead bullet, and lead could no longer be found in the urine. Likewise, they had under observation two patients with anemia (2,800,000 and 3,200,000 red blood cells respectively) in whose erythrocytes basophilic granulation was observed. These patients were also benefited by extraction of lead bullets. The authors believe, therefore, that lead bullets or bits of shrapnel, which are not causing trouble locally, may, nevertheless, be responsible in some cases for toxic effects whose nature should be suspected.

Experimental Studies in the Etiology of Acute Epidemic Poliomyelitis.—J. W. NUZUM and M. HERZOG (*Jour. Am. Med. Assn.*, 1916, lxvii, 1205) report bacteriological studies of the recent epidemic of acute poliomyelitis in Chicago. All of their material was obtained from the Cook County Hospital. They have obtained a Gram-positive micrococcus from the tissues of the central nervous system, tonsils, mesenteric lymph glands, and from the cerebrospinal fluid obtained during life. Cultures of this organism, when injected in monkeys, produced the typical clinical and pathological picture of acute poliomyelitis. Definite flaccid paralysis has been produced in dogs and in many young rabbits. The organism grows better aërobically than anaërobically. Anaërobic cultures in fluid mediums were passed through Berkefeld filters V, and inoculations of the filtrate into suitable mediums produced a growth of the larger form of the organism seen in aërobic cultures. In the tissues from the central nervous system of poliomyelitic material preserved in 50 per cent. sterile glycerin, this same micrococcus was alive after a period of thirty-five days, and could be cultivated in pure culture on suitable mediums.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

The Surgical Treatment of Perforated Ulcer of the Stomach.—WILENSKY (*Ann. Surg.*, 1916, lxiv, 403), says that the ideal method of operative treatment would comprise the closure of the perforation plus some procedure for the cure of the underlying ulceration. The feasibility of doing anything further than a purely life-saving measure is determined by the general condition of the patient at the time of the operation and by the extent and degree of the associated peritonitis. Nineteen cases were operated on for this condition. All were between twenty-five and forty-five years of age. Nine died (47 per cent.). The absolute indications for the addition of gastro-enterostomy to the closure of the perforation at the primary operation are given as follows: (1) Stenosis of the pylorus or duodenum, which may result from old or recent peripyloric or periduodenal adhesions. (2) To safeguard the stitches. (3) When the perforation is only packed or drained, gastro-enterostomy, with unilateral exclusion of the area of perforation, is the only safe way of preventing the formation of a duodenal fistula. The development of such a condition (and if nothing is done for its prevention it will almost invariably develop) is a most serious end, in the great majority of the cases, a fatal lesion. Gastro-enterostomy also offers the following advantages: (1) It facilitates the early nutrition of the patient. (2) It exerts a favorable influence upon the underlying ulcerated condition. (3) It diminishes the danger of subsequent hemorrhage or perforation in coexisting ulcers and favors the healing. The following objections have been made to the addition of a gastro-enterostomy at the primary operation: (1) It prolongs the operation and adds to the shock. (2) It spreads infection to uninvolved portions of the general peritoneal cavity and into the lesser peritoneal sac. (3) Gastro-enterostomy is not necessary because, in the first place, it does not always cure the underlying condition; and, in the second place, patients recover from the ulcer without it. (4) The performance of a gastro-enterostomy at the primary operation adds to the mortality. Of Wilensky's series, 9 died; of these 3 had had gastro-enterostomy made at the primary operation. Of these 3, 1 died of shock, 1 of pneumonia on the seventh day, and the third died on the thirty-third day from a perforation of a coexisting ulcer. Of 8 patients treated by simple closure, 5 died. Of 10 patients treated by closure and immediate gastro-enterostomy, 3 died. Of 1 patient treated by tamponade, 1 died. Wilensky believes that, excluding the moribund cases, gastro-enterostomy is a most valuable procedure, not only as a help in securing the closure of the perforation, but also as a measure directed toward the underlying condition.

A Report of Nine Consecutive Operations for Perforated Gastric and Duodenal Ulcers.—Shea (*Ann. Surg.*, 1916, lxiv, 410) says that all of the cases recovered. When seen early the diagnosis is easy. A positive diagnosis before operation was made in 8 cases. The most pronounced and characteristic symptom was pain—sudden, violent, and continuous. The abdomen was flat, retracted, and the rigidity board-like. The facial expression showed great distress and the respirations were shallow and rapid. In 5 cases the patient vomited, but this greatly increased rather than lessened the distress. Six patients gave a history of gastric disturbance, 3 gave no history of gastric trouble whatever. On opening the abdomen, when the perforation was found, the opening was cauterized with the actual cautery, a purse-string inserted, which, when drawn tight, readily closed the opening. In all cases drainage was provided. When there was considerable escape of fluid, the pelvis as well as the local site of perforation was drained. Contrary to the procedure of many operators, no attempt was made to perform immediate gastro-enterostomy, because it was thought the added shock would prove detrimental in many cases, and also because it was felt that many cases of gastric ulcer recover after perforation. It is noteworthy that the majority of the patients remained free from subsequent gastric disturbances after treatment.

The Interpretation of Functional Renal Tests with Special Reference to the Significance of Minimal Excretion of Phthalein and Indigo-carmin.—Beer (*Ann. Surg.*, 1916, lxiv, 434) says that the last word in functional renal tests is still far off. The practical value of these tests becomes more and more evident as one succeeds in improving the interpretation of the facts elicited. In research along these lines one encounters puzzling contradictions, and it will take much more work to explain many of them. Why a given kidney (*e. g.*, a case of ureter stone) secretes more urea than its mate, but fails to excrete indigo-carmin while its mate does it normally, or why a patient dies of uremia while the phthalein output is normal or almost normal, illustrate some of the perplexities that one encounters. The important practical point in Beer's work is to arrive at an understanding of the significance of zero or minimal excretions. From a study of 17 cases, he concluded that: Extrinsic causes (usually obstructive in character) may lead to permanent symmetrical renal damage, evidenced by minimal or zero excretion of phthalein or indigo-carmin associated usually with high blood urea and high incoagulable nitrogen blood content. Operation in these cases will be of no permanent benefit, and even the slightest (in one case the passing of a cystoscope) may bring on a fatal uremia. Similar extrinsic causes may lead temporary renal damage evidenced by the same phenomena. Operation in these cases, particularly after adequate preliminary treatment, will be rarely followed by uremia. These two wholly different types of cases can be differentiated by removal of the usual causative factor, *i. e.*, relief of the obstruction, either by use of indwelling catheter, of regular catheterization, or by preliminary cystostomy under local anesthesia or gas. If the case is of the first type, no marked change in the renal output will result, whereas if the case is of the second type, the renal output will regularly improve. A similar low combined output may be caused reflexly (inhibitive or toxic) by more or less extensive disease of one kidney, while the other kidney is adequate and improves in its function after removal of its diseased mate or after relief of the pathological condition in its mate. A low combined output may also be due to bilateral intrinsic causes and improvement in these cases is possible only after operative attack on the kidneys, or the kidney, if single, under an anesthetic which has no injurious effect on the diseased parenchyma and provided no severe wound infection or other septic complications, etc., which overtax this parenchyma, develop.

The Treatment of Genital Tuberculosis in the Male.—Cunningham (*Surg., Gynec. and Obst.*, 1916, xxxiii, 3825) says that the material upon which his communication is based is from the postmortem and clinical data of the Boston City Hospital; the Long Island Hospital, where there is a large tuberculosis camp; private cases; and a survey of the literature. In 4250 autopsy records he found 35 instances of tuberculosis of the epididymis, the most common lesion of the genital tract to be observed clinically, in which a microscopical examination as well as a gross description of the condition of the prostate and vesicles is recorded. He found 86 clinical cases of tuberculous epididymitis. A consideration of the literature, both postmortem and clinical, shows that tuberculosis of the genital tract in the male, is most common in the epididymis, and from the epididymis the disease extends along the vas, either by continuity or lymphatics to the vesicles and prostate. The postmortem and clinical findings show that the great majority of cases of genital tuberculosis have active tuberculosis elsewhere in the body, the infection in the genito-urinary tuberculosis being a secondary one. It must be considered that the majority of cases of tuberculous epididymitis have tuberculosis of the vesicles and prostate on the corresponding side, whether the condition can be demonstrated by physical examination or not. Cases of genital tuberculosis often have associated tuberculosis of the bladder and kidney, and a cystoscopic examination with catheterization of the ureter should be a rotation procedure, in each case, before the possibility of such associated infection can be eliminated. In the opinion of Cunningham, the best treatment for the local condition, in most instances, is to remove the scrotal focus by epididymectomy or castration, and this should be followed by injecting the vas with a dram of crude carbolic acid, with the hope of eradicating the disease from the genital tract. The destruction of the local focus is but the first step in the process of immunizing the patient against fresh outbreaks of the disease; and the hygiene and tuberculin should be made use of indefinitely, as they serve further to aid in a rational way, the immunizing power of the body against remaining lesions.

Perforation in Typhoid Fever. — Eddy (*Surg., Gynec. and Obst.*, 1916, xxxiii, 451), from a report of one case and an extensive study of the literature, concludes that: While perforation varies greatly in different epidemics, about 12 per cent. of the total death-rate is due to this complication. Perforation occurs in about 3 per cent. of all cases treated. It is relatively infrequent in children. Statistics show that 80 per cent. of total perforations occur in the lower ileum. The majority of cases perforate during the second and third week. Diarrhea is an important factor in its production. Acute abdominal pain in the course of typhoid should always be taken seriously. The sudden rise of blood-pressure is positive evidence of perforation, while an unchanged pressure is not of negative value. The importance of a careful study of the blood cannot be overestimated. The welfare of the patient depends upon our ability to differentiate between the symptoms of perforation and those of the resulting peritonitis. The treatment of perforation is surgical, and the death-rate is in inverse ratio to the length of time allowed to elapse before operation. Opiates are indicated as soon as perforation has taken place and should be continued until the peritonitis has become well localized.

The Treatment of Fractures by Nail Extension.—Dyas (*Surg., Gynec. and Obst.*, 1916, xxxiii, 478), on the basis of five cases treated by this method and a study of the literature, says that Steimann's nail extension in the treatment of fractures is less dangerous than the radical open operation. It enables the surgeon to exert the maximum amount of traction while using the minimum area for the attachment of the traction apparatus. It will bring about a reduction of the deformity in old cases where other methods fail. The technic is not difficult and can be mastered by anyone. Therefore the method is practical and can be used by the entire profession. It gives access to wounds in compound fractures, permits of infrequent dressings, and does away with unclean, infected fixation apparatus. The apparent brutality of the procedure is not real as the patients suffer no more by this traction than by any other method. The danger of infection is less than the danger of an open, radical operation. Hemorrhage may occur but can always be readily controlled by enlarging the incision and tying off the bleeding point.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

Splenectomy in Pernicious Anemia.—Lee, Minot and Vincent (*Jour. Am. Med. Assn.*, 1916, lxvii, 719) give their findings regarding the mode of action of splenectomy as a therapeutic procedure—particularly with regard to its effect in stimulating the bone marrow to produce new blood. They believe that splenectomy in pernicious anemia has in nowise a specific stimulating effect on any one portion or any one function of the bone marrow. It apparently acts grossly on all portions, though the effects are seen at different periods of time in relation to the operation. They attribute the temporary improvement in pernicious anemia after splenectomy to two factors: (1) an associated diminution in the blood destruction; and (2) the associated increase in activity of the bone marrow. They do not attempt to explain the precise mechanism by which splenectomy brings about an increased activity of the marrow. Certain stimulating effects after splenectomy are seen almost immediately, as in the case of the increase in the polymorphonuclear leukocytes. The increase in the platelets tends to occur somewhat later, and the main increase of the reticulated cells, when it occurs, seems to be inaugurated still later. This effect on the part of the bone marrow which forms red cells is much more difficult to bring about and also is slower. Splenectomy seems to result in the greatest stimulation of the bone marrow of any known therapeutic measure. It acts on the whole bone marrow and not only on the portion that forms red cells. However, splenectomy does not alter the essential course of the disease. While more constant stimulating effects are seen after splenectomy, yet they can roughly parallel any individual case of bone marrow stimulation after splenectomy with a case of bone marrow stimulation that occurred either spontaneously or after transfusion. It is evident that from splenectomy one can attain stimulation but once. Transfusion, while perhaps of less constant and of less active effect, has two great advantages. It is relatively simple and can be repeated a number of times. Transfusion does not modify the destructive agencies at work in pernicious anemia. These considerations must be carefully weighed in advising any therapeutic procedures in this disease.

The Use of Emetin.—Reid (*Bost. Med. and Surg. Jour.*, 1916, clxxv, 375) says that the predominant use of emetin is in the treatment of amebic dysentery, and the history of the empirical use of ipecac, combined with the demonstration of the specific amebicidal action of emetin, places its use here on a solid footing. In using emetin in dysentery it is important to recall that if there is to be any benefit, it will usually appear early, ordinarily by the third or fourth day. Emetin seems specific in direct proportion to the acuteness of the attack. Chronic dysentery and ameba carriers, as a rule, are influenced by emetin directly, although even here there are certain favorable reports. Emetin has also a very definite use in the presuppurative stage of amebic abscess of the liver. After actual abscess formation, emetin may be a valuable adjuvant to surgical treatment. Emetin has been advocated lately for the treatment of pyorrhea. It will, without doubt, cure the amebic infection found associated with pyorrhea but definite proof that amebæ are the cause of pyorrhea is still lacking. The use of emetin as a remedy for hemoptysis in pulmonary tuberculosis apparently originated in France. Certain clinical observations seem to justify the belief that emetin is a useful drug in hemoptysis but the treatment is entirely empirical and does not rest upon any solid foundation. Emetin has been tried and recommended for a great variety of diseases but very few of its other applications will bear the test of careful experimentation. It has proved serviceable in the treatment of certain other diseases caused by animal parasites, especially protozoöns, but the chief use of emetin is dependant upon its amebicidal action.

Peripheral Neuritis following Emetin Treatment of Amebic Dysentery.—Wilgore (*Bost. Med. and Surg. Jour.*, 1916, clxxv, 380) reports seven cases of peripheral neuritis following the use of emetin in amebic dysentery. He says that peripheral neuritis after emetin is not uncommon. The symptoms most commonly met with in postemetin neuritis are muscular pain and weakness, usually most pronounced in the legs, sometimes going on to paresis. The neuritic symptoms often develop after the emetin injections have been stopped, and may grow progressively worse for some time, with no more administration of the drug. The total amount of emetin necessary to produce neuritis varies greatly. The prognosis is good; the symptoms clear up gradually, usually over several weeks, leaving no traces apparent. Experiments, made by Wilgore, suggest that peripheral neuritis may be produced in healthy dogs by emetin.

Three Cases of Entameba Histolytica Infection Treated with Emetin Bismuth Iodid.—LAW and DOBELL (*Lancet*, 1916, cxci, 319) say that evidence derived from their own cases and from cases reported by Dale has convinced them that emetin bismuth iodid is far more efficacious than emetin hydrochlorid, given hypodermically, in removing the cysts from the feces of chronic carriers. The authors recommended giving the remedy in a single dose of three grains—this representing a little more than one grain of emetin—once a day with the evening meal, and never on an empty stomach, as was customary with ipecac. Such a dose is to be given on five successive days—and the full course of treatment recommended is twelve doses of three grains each. One disadvantage is that this new emetin compound produces much more disagreeable symptoms than emetin hydrochlorid given by the needle. Nausea, vomiting and diarrhea were the untoward symptoms produced. Three cases are reported in detail as types of amebic infection for which method of giving emetin is recommended.

Late Results of Splenectomy in Pernicious Anemia.—KRUMBHAAR (*Jour. Am. Med. Assn.*, 1916, lxvii, 723) says that the striking improvement that has been shown to follow removal of the spleen in such diseases as hemolytic jaundice and Banti's disease has naturally led to an extension of this clinical procedure to allied conditions. In 1913 three investigators, Eppinger, Decastello and Klemperer, working independently, applied splenectomy to the relatively common and grave disease, pernicious anemia. It is interesting that Eppinger was led to adopt this procedure by observing after splenectomy a diminished output of urobilin and other evidences of decreased hemolysis. Decastello, on the other hand, had noted the improvement that followed splenectomy in the related conditions, hemolytic jaundice and Banti's disease; whereas Klemperer was influenced by the clinical observation that splenectomy for such conditions as rupture of the spleen was in some instances eventually followed by polycythemia. Krumbhaar reviews critically the reported cases of splenectomy as a therapeutic measure for pernicious anemia in order to determine how valuable splenectomy has thus far proved to be in pernicious anemia. Of the 153 patients studied, 19.6 per cent. died within six weeks; a distinct improvement in the clinical condition and in the blood picture occurred in 64.7 per cent., and no improvement in 15.7 per cent. The rather high postoperative mortality (practically 20 per cent.) may be due to poor choice of cases in the early series. As a much greater proportion of the more recent cases has survived the operation, the true postoperative mortality is probably much less than 20 per cent. Of the individuals who showed improvement shortly after operation, nearly two-thirds of the total number, a large number have failed to maintain this improvement, or have since died in a relapse or from intercurrent disease. Although a few have continued in good condition during the period of observation (over two years), in no case can it be said that a cure has been effected, and the blood of these individuals continues to show many of the characteristic signs of pernicious anemia. On account of the improvement that follows splenectomy, it would appear to be not only a justifiable, but in many cases an advisable, procedure; but in no case should a cure be promised or the operation undertaken except under the most favorable conditions. The best results are obtained if the operation is preceded by one or more transfusions, and those patients who relapse after operation may still be greatly helped by transfusion. Whether or not transfusions would have produced equally good results in the absence of splenectomy is a question that cannot at present be decided. The most favorable results may be expected in individuals who have not passed the fifth decade in whom the disease has not progressed for more than a year, and who have a relatively good blood picture (that is, an anemia that is not of too extreme a degree or of the steady, progressive type). Individuals with enlarged spleens have done better than those in whom the spleen was small or of normal size, as have also those suffering from an anemia characterized by excessive hemolysis. The opposite of these conditions should be considered as unfavorable factors, as should also the existence of spinal cord symptoms or the presence of an aplastic bone marrow.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND FREDERICK O. WAAGÉ, M.D.,
OF PHILADELPHIA.

A Case of Egg-poisoning (Anaphylaxis).—Edleston (*Practitioner*, vol. xcvii, No. 4) reports a well-marked case of egg anaphylaxis, first noticed at the age of twelve months. The first attack began after taking a few teaspoonfuls of custard pudding. The symptoms were those of an acute gastritis with frequent vomiting. She was given albumen water and rapidly collapsed. All food was then withdrawn, and later chicken broth was substituted, under which treatment she soon recovered. Eggs in every form were avoided after this, but on several occasions when given accidently, the symptoms have usually been as follows: The child complains of feeling ill, and wants to lie down; the pupils dilate, and vomiting follows. In some attacks chemosis of the conjunctivæ supervenes. Urticaria has occurred in some of the attacks. On one occasion, while standing near her mother, who was beating an egg on a plate, a splash of egg flew into her eye. This was followed by rapid swelling, so that the eye could not be opened, but no other symptoms of poisoning followed. The child is now eleven years old, and is still as sensitive as ever to the poison.

A Case of Prolonged Hyperpyrexia in a Child with a Mid-brain Tumor.—Turner (*Brit. Jour. Child. Dis.*, September, 1916) reports an unusual instance of prolonged hyperpyrexia associated with a tumor in the mid-brain. The child, aged one year and six months, was admitted to the hospital with the provisional diagnosis of meningitis. There was opisthotonos, squint, and convulsions on the day of admission. Hydrocephalus was present, the fontanelle being very tense.

Temperature was 103° on admission, pulse 172, and respirations 60. About two and a half ounces of clear colorless fluid was withdrawn by lumbar puncture, under great pressure. The fluid showed no increase in albumin; no cells were seen, and the cultures were sterile. The child lived for thirty days after admission, in a state of extreme rigidity. Lumbar puncture was repeated twice, the cells, mostly mononuclears, being more numerous than normal. The Wassermann reaction was negative. There was a low grade optic neuritis. The temperature was the most remarkable feature of the case. For a period of ten days it showed very great variation; once, or sometimes twice during twenty-four hours it would rise to 105°, 106° or 107°, and then rapidly falls so that in eight to twelve hours it would be normal or subnormal. The maximum was reached one morning at 7 A.M. when the axillary temperature was 109°, and the rectal 111°. Postmortem a solid rounded tumor was found situated in the mid-line in the region of the corpora quadrigemina. It did not involve the pons, optic thalami, or the cerebellum, but was pressing forward into the aqueduct of Sylvius, causing a block, with resulting distention of the third and lateral ventricles. Microscopically the section of the tumor showed it to consist of numbers of round cells, uniform in size, with but little intercellular substance. In parts the growth had undergone cystic degeneration, leaving a hyaline material without cell element: The author was unable to find a similar case recorded in the literature, and apart from the terminal hyperpyrexia of cerebral lesions, there is no mention to be found of any such condition occurring in cases of cerebral tumor.

The Bacteriology of the Urine in Healthy Children and those Suffering from Extra-urinary Infections.—BEELER and HELMHOLZ (*Am. Jour. Dis. Child.*, October, 1916) report their bacteriological findings of catheterized specimens of urine taken from thirty girl infants and from thirty-one girls over two years of age. In 118 specimens of carefully catheterized urine from these 61 girls, 61 were sterile and 57 contained bacteria. Of those from normal infants, 13 were sterile and 11 contained bacteria. Of those from extra-urinary infections in patients under two years of age, none were sterile and 24 contained organisms. In those from girls over two years, 38 were sterile and 22 contained bacteria. The number of bacteria found in the urine of children under two years was considerably larger than in those over two years. This may be explained by the fact that in the older children one can cleanse the urethral orifice much easier than in the infant and introduce the catheter directly into the urethra. The bacterial flora was practically the same in both series, Gram-positive cocci and diphtheroid organisms predominating, the former being present in practically every case in which any organisms were found. In no instance were Gram-negative bacilli found in such numbers in both specimens that it seemed probable that it was more than an accidental contamination from the urethra. The conclusions the authors draw are, (1) that organisms of the colon bacillus group are not normal inhabitants of the female urethra; (2) that in extra-urinary infections occurring in the first two years of life the colon group of bacilli are frequently found in the urethra (one-third of the cases); (3) that in girls over two years of age the urine is almost free of organisms, and in their series entirely free from bacilli of the colon group (eighteen normal, twelve other infections).

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Modern Obstetric Surgery.—Munro Kerr (*Brit. Med. Jour.*, July 15, 1916) has recently published a third edition of his book on midwifery. This book gives an excellent account of modern obstetric surgery from the English standpoint. Where tetanic contraction of the uterus occurs in complicated labor, the question arises as to what method of delivery is safest for mother and child. To the obstetrician, Cesarean section in clean cases where the child is living, suggests itself as the best method of treatment. Where, however, the case is not clean, or suspected, a full dose of morphin and atropin are first given, followed by an interval of rest, and then delivery by craniotomy. Fibroid tumors complicating pregnancy must be managed in accordance with the size and location of the tumor and other conditions present. Wherever possible enucleation is preferred. Upon one important subject the author speaks with decision. Appendicitis during pregnancy, labor, or the puerperal period is considered a highly dangerous complication. The author would treat all such cases on strictly surgical lines without regard to the existence of pregnancy. In this the reviewer fully agrees, and his opinion is based on experience and clinical observations. While the proposition to enlarge the pelvic girdle by operation is in some respects attractive, the procedure has a limited field of usefulness, but it is only in exceptional cases that good results will be obtained. One of the most difficult problems for the obstetrician is the management of a case requiring delivery by section where the child is alive and the mother infected. Shall one choose craniotomy upon the living child or shall one deliver by section followed by hysterectomy? The author is convinced that craniotomy should sometimes be chosen even though the child is alive. He raises the question whether hysterectomy really saves mother and child. He believes that we do not save mothers, for the maternal mortality from hysterectomy and craniotomy in infected cases is almost identical. A few children are saved by hysterectomy, but young mothers may be sterilized who losing the first child might subsequently produce several others. The flaw in this argument lies in the fact that Kerr has evidently not left the stump of the septic uterus outside the peritoneal cavity in treating these infected cases. Hysterectomy, followed by dropping of the septic stump, has a very considerable mortality from sepsis, while hysterectomy followed by leaving the stump outside the peritoneal cavity, whether it be stitched into the tissues or held by a clamp, has a very low mortality. For the various kinds of extraperitoneal section and section through a peritoneal fistula he has no praise. He has had no experience, believes that this method has no advantage over classical section, and will disappear and be forgotten unless experience shows that the scar in the lower segment is much stronger than the one in the upper part of the body of the uterus. One would scarcely expect, in the present condition of affairs, an operation largely perfected in Germany to be popular with a British obstetrician. The author regards vaginal Cesarean section as an operation of great value, but used too freely. Up to the twenty-fifth week of pregnancy it is the best way of rapidly emptying the uterus, after the abdominal route is preferred. Vaginal section should never be chosen in placenta previa. The author would perform abdominal Cesarean section in placenta previa in elderly primiparæ with active bleeding, undilated cervix, and viable child. Despite the recent literature upon the subject, in accidental hemorrhage the author clings to the tampons where the membranes are intact, and the bleeding external, but what he would do when the placenta separates with retained blood, is not clear. He does, however, condemn the use of the bags, the Bossi, and similar dilators. He admits that in concealed hemorrhage section may be necessary, and prefers vaginal operation. In the field of English obstetrics Kerr's book is easily the best upon obstetric surgery, and we welcome a new edition and learn with great interest the views of this author.

The State and the Birth Rate.—The question of what can be done to prevent a falling birth rate has been recently studied by the authorities of the British Empire, and the local government board has recently received the report of the commission appointed to inquire into the decline of the birth rate of England. In the London letter to the *Journal of the American Medical Association,* dated July 3, 1916, and published in the *Journal* for July 29, 1916, it is stated that this report advised that the sale of certain drugs widely used for the purpose of abortion should be made illegal. Measures must also be taken to lessen the ravages of venereal disease. The most difficult problem consists in educating the public opinion to condemn effectively vice which brings about disease. It is also necessary to improve the living conditions and adjust the burdens of taxation for that class of the population capable of producing the best children, and caring properly for them. The large, and socially valuable middle class should receive especial attention from this standpoint. It is also urged that immigration to healthy portions of foreign possessions be encouraged, and the taxation should be adjusted as to bear least heavily upon those who are rearing families.

An Infant Mortality Rate of Zero.—A community in which the infant mortality has been reduced to zero presents much of interest in view of the increased value at present attributed to infant life. In a paper published in the London *Lancet,* May 6, 1916, Moore, an English medical health officer, learned that Villiers-le-Duc, a little commune in the south of France, had an infant mortality rate of zero for ten years. This seemed incredible, but on applying to the French Academy of Medicine, official documents showed that between 1893 and 1903 no child under one year of age had died in this commune, and no mother had died in childbirth. The infant mortality for the preceding ninety years had been from 20 per cent. to 30 per cent. except from 1854 to 1863, when it fell to 15 per cent. During this time a mayor was elected who was interested in public health and the care of children, and although not a physician he did his utmost for the health of the people. The low death rate just described has been obtained by the son of the former mayor, who studied medicine to obtain knowledge with which to carry out plans for the welfare of the people. In this commune every pregnant woman, married or unmarried, who needs help can apply to the village authorities, and must do so before the seventh month. The patient may select a competent midwife, who must examine her, and if albuminuria, abnormal presentation, or other abnormalities be discovered the midwife must notify the village authorities, who then causes the patient to select a physician. If the patient remains in bed six days after her confinement she has an allowance from the village for her expenses for each day. Mothers or nurses who can show a healthy nursing child a year old are entitled to municipal grants. Other regulations were .made providing for the sterilization of milk and the welfare of infants placed out to nurse. It is true that these statistics are obtained in a small village with simple rural conditions, nor are the statistics available of the population, number of births, and changes in population due to immigration. These facts make the statistics less valuable and others more accurate. They are, however, still interesting, and the simple regulations enforced and their success are certainly suggestive.

The Internal Secretion of the Pancreas in its Relation to Pregnancy.—Falco (*Annali di ostetricia*, No. 1, 1916) has made researches upon animals in the pregnant condition, extirpating the pancreas and then studying the condition of the animal. He finds that the removal of the pancreas seems to diminish somewhat the growth in function and activity of the cells in Langhan's layers of the syncytium. The extirpation of the pancreas does not cause pregnancy to terminate, nor does it produce glycosuria. It naturally produces the symptoms of pancreatic diabetes. This does not seem to influence the internal secretion of the fetal pancreas, as evidently the abnormal products formed in the mother's body are disposed of by the fetus and by the placenta. The placenta evidently has an important part in the disposition of physiological products in the mother and fetus.

Viburnum Prunifolium to Prevent Abortion.—In recent numbers of the *Journal of the American Medical Association* has appeared the testimony given in a suit brought against the *Journal* in which various statements are made concerning the efficiency of viburnum in preventing or checking abortion. The reader of these conflicting statements must judge for himself. So far as the reviewer's experience goes he has no positive and accurate evidence that viburnum prevents or stimulates uterine contraction, or prevents or stimulates abortion. He has used it, but always in compounds with other drugs whose actions are well known. So far as his experience goes two medicinal substances lessen or prevent contraction of the uterus. One comprises that class acting as sedatives to the general nervous system, of which bromide of sodium is a good example. The other is opium, the most reliable drug which we possess in preventing uterine contraction and lessening its vigor.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Carcinoma of the Uterus in a Child.—A most remarkable case of adenocarcinoma of the uterus occurring in a child two and a half years of age has been reported by Adams (*Brit. Jour. Child. Dis.*, 1916, xiii, 266). The parents were healthy, and this was their first child. It appeared healthy and well nourished, but for three weeks before admission to the hospital there had been a bloody vaginal discharge, increasing in amount. There was no pain, but the mother had noted some fulness of the abdomen; on examination a palpable tumor was found in the hypogastrium, lying apparently between the bladder and rectum. At operation a rounded, cystic growth, the size of half a tennis ball, was found obscuring the position of the uterus. A portion of the mass was removed, but it was too adherent to permit of complete extirpation. The vaginal hemorrhage reappeared shortly after the operation, gradually increasing in amount; the child lost ground steadily, and died in two months. At autopsy a large mass was found occupying the centre of the pelvic cavity, closely adherent to the bladder and rectum, representing the uterus, which was in large part transformed into breaking-down tumor tissue. Histologically it proved to be a carcinoma apparently arising from the glandular epithelium of the corpus uteri. At one point the growth had penetrated the bladder wall. Unfortunately the author presents no illustration of either the gross or microscopic appearances of this remarkable specimen.

Radium Treatment of Uterine Cancer.—Practically all reports upon this subject from this country must be considered as more or less preliminary at present, as very few workers can report cases of five years' standing or longer; it is well, however, that results should be recorded from time to time as the work in various clinics progresses, provided the reports are modified as time goes on. Taken, therefore, purely in the light of a preliminary report, a recent short paper by J. and J. L. Ransohoff, of New York (*Ann. Surg.*, 1916, lxiv, 298), presents some exceedingly encouraging results so far, none of their cases having been followed for more than two years, however. They report having used radium in 25 cases of uterine carcinoma; of these, 11 appear clinically well, 3 of these having been followed for two years, the remainder for periods of six months to almost two years. Of these 11 cases, 8 were inoperable, and 3 were operable from a technical stand-point, but because of other conditions operation was considered inadvisable. Even in the cases where a clinical cure was not obtained, some benefit was obtained in every instance, the experience of these authors in this respect having been apparently more fortunate than that of most other workers with radium, nearly all of whom report a certain percentage of cases in whom not only no benefit, but even some apparent harm, is seen following treatment. The authors report a couple of instances in which there was almost magical disappearance of extensive vaginal masses, with correspondingly great improvement in the patient's general condition. In a few instances the patients have complained of pain in the rectum, sometimes quite severe, coming on subsequent to radium treatment. The authors suggest that this may be due to the formation of scar tissue, though this they cannot definitely demonstrate. They advise very strongly against attempting radical operation in cases clinically cured by radium.

Cystitis in Elderly Women.—Under the title "Cystitis Senilis Feminarum," CHARLTON (*Surg., Gynec. and Obst.*, 1916, xxiii, 371) calls attention to a condition which he considers to be an important clinical entity, but which has received very little attention in the literature, namely a peculiar type of cystitis, presenting characteristic cystoscopic changes, and occurring with very few exceptions in elderly primiparæ. The history is usually that a woman well past the menopause, mother of several children, in fairly good general health, gradually begins to notice undue frequency of urination, with burning and tenesmus. There is no acute onset, but from time to time there may be severe exacerbations, causing marked impairment of the general health. Such sharp attacks may persist for weeks, followed by months of comparative comfort. The urine may show a moderate amount of mucus, with some pus, but is never grossly thick and ropy. Bacterial findings have been entirely inconstant, and the tubercle bacillus does not appear ever to be the causative factor. The author believes, therefore, that it is probably not due to a specific infection, but is a condition developing after many different bacterial onslaughts in bladders already weakened by the process of senile decay. He has found that almost without exception the condition is common to the bladder, vagina, and rectum simultaneously. The vaginal changes are those of ordinary senile vaginitis. The rectal mucosa varies in its appearance in these cases from multiple punctate erosions to large distinct punched-out areas of ulceration on an otherwise normal pink velvety base. The cystoscopic appearance is primarily that of numerous vesiculopapillary elevations, seen especially during the acute exacerbations, and presenting the picture commonly designated as bullous edema; in two cases the similarity to miliary tubercles was striking. During the interval the vesicular eruption disappears and gives place to a patchy, ecchymotic appearance of the bladder mucosa, with unbroken epithlium. The treatment of these cases is best carried out, according to Charlton, as follows: (1) The best of general and hygienic care. (2) Hot boric irrigations of the bladder, which may be supplemented with instillations of argyrol. Vigorous local treatment, such as the application of strong silver solutions, is to be condemned. (3) Alkaline vaginal and rectal douches. (4) Administration by mouth of *pure liquid guaiacol,* given in 5- or 10-drop doses after each meal. This drug the author has found to possess almost specific properties; it almost always brings remarkable and quick relief from the frequency of urination, tenesmus, and burning of which these patients complain so bitterly. Its use is largely empiric, though an attempt has been made to explain its effect on the ground that the benzoic acid radical is broken up and eliminated by the kidneys as hippuric acid, which being a normal urinary acid may play some definite part in the relief.

OPHTHALMOLOGY

UNDER THE CHARGE OF
EDWARD JACKSON, A.M., M.D.,
DENVER, COLORADO,
AND
T. B. SCHNEIDEMAN, A.M., M.D.,
PHILADELPHIA.

Optic Nerve Atrophy in Chiasmal Lesions.—Walker and Cushing (*Arch. Ophth.*, xlv, 407), from their studies in this condition, conclude that, despite the so-called atrophic pallor of the disks with visual field defects from lesions in the chiasmal regions, the histological examination of the nerves fails to show the expected degree of fiber degeneration unless the process has been of long duration. The atrophy in the tracts considerably antedates that in the nerves, where the fibers may be preserved by their retinal ganglion cells for several years after complete functional blindness has occurred. Their cases serve to illustrate the fact that in the presence of chiasmal pressure of known long duration associated with sharply cut hemianopsias, even when the ophthalmoscope shows the pallor of presumed optic atrophy, there may be no corresponding sharp delimination of the areas of atrophy in the cross-sections of the nerves. This at first sight would appear to be an inconsistency, but their more accurate perimetric findings with graded disks show that, after all, the boundaries of the seeing areas are less sharply cut than had previously been supposed, and perhaps correspond after all with the diffuse picture in the nerves.

Hemeralopia (Night-blindness) in Soldiers.—Weekers (*Arch. d. Ophth.*, March–April, 1916, p. 73) calls attention to this condition as a novel phenomenon of war. He finds that it is frequent among soldiers—as high as 10 per cent. of those sent for ocular complaints. The cases are specially numerous during the long nights of winter. Errors of refraction are frequent. Many had been affected with the same condition as a congenital anomaly before the outbreak of the war. The malady is provoked by several factors, although of unequal importance. First of all is to be noted the unphysiological mode of life in the trenches which is nocturnal, fatigue, nervous upsets, anxiety, overexertion. Eye-strain from errors of refraction is also an important factor. Finally, the unvarying diet, preserved foods, dazzling from bright lights, etc., are also involved. The treatment should be directed to the cause. One of the most efficacious means is careful correction of all refractive errors especially astigmatism: smoked glasses during the day form a valuable adjuvant. Varied diet and as much rest as possible should be prescribed. The prognosis is favorable.

A Suggestion as to the Cause of Myopia.—Wood (*Ophthalmoscope*, 1916, xiv, 302) suggests that the marked difference between the ciliary muscles of the myope and hypermetrope may be the cause of the myopic refraction and not the effect as is generally believed. He quotes authorities to the effect that the difference in structure is present at birth and hence cannot be the result of disease, mechanical pressure, or disuse. He argues that the pumping action of the ciliary muscle is at fault, and that it is this which favors the changes which lead to brachymetropia. He remarks upon some of the causes (strain of convergence, spasm of accommodation, etc.), frequently adduced as leading to myopia, and believes that the progress of investigation has disposed of most of them. He thinks that if sections from the eyes of an individual with monocular myopia were to show a difference in the ciliary muscle on each side, his case would be greatly strengthened. Such cases can assuredly be found, and deserve to be studied pathologically.

Contusion Hypotony.—Collins (*Ophthalmoscope*, 1916, xiv, 348) discusses that form of hypotony which occurs after contusions of the eyeball without perforation; this form of minus tension is well-known but has been the subject of but little discussion. The duration of the diminished tension varies considerably; in the majority of cases it disappears in a few days; in others not for several weeks; and in some cases it would appear to be permanent. The causes of such hypotony may be various and more than one cause may be active at the same time. When of short duration, it is probably due to increased excretion of the intraocular fluid through the expanded normal channels of exit; or, possibly, to some arrest of secretion from paresis of the vasoconstrictor nerves. When of long duration it may be due to (*a*) the formation of new channels or exit from the anterior chamber either from an internal scleral rupture or rupture of the pectinate ligament; (*b*) the cutting off of blood supply to the ciliary body from rupture of the anterior ciliary arteries; or (*c*) possibly detachment of the pars ciliaris retinæ. If extensive hemorrhage into the anterior chamber be present, either the canal of Schlemm has been opened by an internal scleral rupture or the anterior ciliary arteries have been torn across from cyclodialysis. The latter is shown to be the cause if, after absorption of the blood, a portion of the iris has disappeared from view as though an iridectomy had been done. A translucent area appearing after some time just outside the sclerocorneal margin like that in a cystoid cicatrix, indicates an incomplete internal rupture. If the anterior chamber, without extensive hemorrhage, becomes markedly deepened in the whole or part of its circumference there has probably been a rupture of the ligamentum pectinatum, limited to the pillars of the iris, and of the ciliary muscle, prolonging the angle of the anterior chamber outward. If the lens is dislocated laterally, and the retina detached, the vitreous has probably come forward into the circumlental space, and may have dragged the pars ciliaris retinæ away from the pigment epithelium.

Miotics after Mydriatics.—Gifford (*Jour. Am. Med. Assn.*, 1916, lxvii, 112) calls attention to the slight but real danger of exciting an attack of glaucoma by the cycloplegic (homatropin) employed to measure the refraction. He suggests that eserin solution should be instilled not only after the examination, but should also be given for use at home until the effect of the mydriatic is gone. He advises that the patient receive a small quantity of eserin solution, one grain to the ounce, a drop of which is to be instilled into the eye with the butt end of a match or toothpick. He reports several cases where an attack of acute glaucoma was excited by the cycloplegic.

Enlargement of the Blind-spot with Gradenigo's Syndrome.—Verderame (*Ann. di ottal.*, 1916, xliv, 538) summarizes Gradenigo's researches which led to the syndrome bearing his name—a disease-complex first described in 1904; the syndrome is characterized by a purulent otitis media with paralysis or paresis of the sixth nerve of the same side. Of the 6 cases observed by Gradenigo, 5 recovered, the other terminated fatally from purulent leptomeningitis. He refers the condition to a circumscribed purulent or simply serous leptomeningitis, which may recover spontaneously, or after operation through the temporal bone, but which sometimes spreads so as to lead to a fatal result. The otitic symptoms are due to infection of the tympanic cavity, which infection may spread to the base of the middle cranial fossa leading to paralysis of the sixth nerve. In a case of this kind, Verderame observed moderate mydriasis, enlargement of the blind spot and slight contraction of the color field; the only ophthalmoscopic signs were hyperemia of the disk and of the retinal vessels. At the end of a week all symptoms had disappeared except the mydriasis; of the significance of which latter symptom the author was in doubt.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,
PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

JOHN F. ANDERSON, M.D.,
FORMERLY DIRECTOR OF THE HYGIENIC LABORATORY, PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Immune Reactions in Scarlet Fever.—In an earlier work, G. F. and G. R. Dick (*Jour. Infect. Dis.*, 1916, xix, No. 2) reported the results of anaërobic culture from the blood, lymph, spleen, throat and mouth secretions in scarlet fever. Before further study of the organisms obtained in these cultures, they decided to test the various tissues from which these organisms were grown in order to determine whether or not a virus either ultramicroscopic or failing to grow with the cultural methods used was present as the primary cause of the disease. The secondary importance of the organisms obtained could then be demonstrated. The following tests were made on the blood and the results noted: Since antigens in the body fluids have been found by means of complement-fixation, this test was applied, but although the tests were carried out in various ways, there was no evidence of complement-fixation. The blood of scarlet fever patients was tested for toxicity by injecting it into guinea-pigs with the result that it was found to be more toxic while the patient is acutely sick than during convalescence. The blood was also tested for the presence of living virus by the potassium tellurid test. In the sera of six cases of scarlet fever there was no precipitation of tellurium more marked than in the negative control tests, although the positive controls showed marked precipitation in every instance. The spleen of a child who had died on the second day of scarlet fever was used to prepare antigen, and complement-fixation tests were made with the sera of six cases of scarlet fever. No tests showed complement-fixation. Cutaneous tests similar to tuberculin tests made with extract from the same spleen in four convalescent scarlet fever patients and four diphtheria patients gave uniformly negative results. In testing the tissue from the lymph glands, an antigen was made from lymph glands from various parts of the body of a patient who had died on the second day of scarlet fever and fixation tests carried on with the same sera as in the spleen tests with uniformly negative results. Cutaneous tests with lymph gland extract were negative in three cases of scarlet fever. In the last series of tests, mucus from the mouth and throat was used as antigen for the complement-fixation tests. In sera from four cases of scarlet fever in various stages of convalescence, each used with a different antigen, there was no complement-fixation. In the fifth case, there was a slight fixation of complement with 0.3 c.c. of antigen, but with the serum of a sixth case, the same antigen failed to fix complement. The results of the complement-fixation tests with organ extracts harmonize with the results obtained by some observers but are at variance with those obtained by others. The authors suggest in their summary that it may possibly be that insufficient concentration of antigen explains the negative results and therefore it seems desirable to further continue the study of the immune reactions of cultures obtained from scarlet fever.

Agglutinins after Typhoid Immunization.—ROBINSON (*Jour. Med. Research*, 1915, xxxii, 417) states that great individual differences occur concerning serum reactions during typhoid immunization. Agglutinins begin to increase in the blood from four to eighteen days after the first inoculation. The blood gives a positive agglutination at 1 to 60, on the average, sixteen days after the first inoculation. ASCOLE (*Riforma med.*, Naples, 1915, xxxi, 645) states that the serum gives a positive agglutination reaction in every one who has been vaccinated against typhoid.

Anaphylactic Reactions between Proteins from Seeds of Different Genera of Plants.—WELLS and OSBORNE (*Jour. Infect. Dis.*, 1916, xix, No. 2) conclude that since chemically similar proteins from seeds of different genera react anaphylactically with one another, while chemically dissimilar proteins from the same seed in many cases fail to do so, we must conclude that the specificity of the anaphylaxis reaction depends upon the chemical structure of the protein molecule.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

JOHN McCRAE, M.D., M.R.C.P.,

LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL; SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL VICTORIA HOSPITAL, MONTREAL,

AND

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Lipoma Myxomatodes.—Although essentially a case report from the standpoint of the pathologist, ROBERTSON (*Jour. Med. Research,* 1916, xxxv, 131) in reality presents a monograph on lipoma myxomatodes The first accurate description of this tumor was that by Virchow in 1857. He included all tumors containing elements resembling the jelly of Wharton or embryonal connective tissue under the term "myxomata," and the particular variety which also showed lipomatous elements he named "myxoma lipomatodes." A tabulated analysis of fifty-one cases collected from the literature is published. In surveying this table, statistical generalizations as to age, sex, sites of election, frequency in such sites and weight of the growth are easily made. It is also known that the usual locations of pure lipomata are singularly free from lipoma myxomatodes. One-third of the cases in the literature have shown malignancy which, in view of the embryonal types of tissue concerned, is to be expected. The statistics show that over half of the cases had existed for one to five years. This would indicate that sarcomatous change had occurred in a primarily benign growth. The tumor in the author's case was removed from the lower leg of a man, aged fifty-four years. It was not connected with the skin and had given no symptoms, although it was present for fifteen months before operation. The tumor was encapsulated. The length was 24.5 cm. and the widest diameter was 6.5 cm., from which the mass tapered down to 2.5 cm. in width at either extremity. The growth was irregularly lobulated, the divisions being formed by fibrous trabeculæ. The various lobules varied widely in consistency. On cross-section, three distinct types of tissue could be identified by gross examination. They were (*a*) myxomatous, (*b*) fatty, (*c*) a mixture of the two. Microscopically, these characters were well borne out. The myxomatous parts showed a stroma of stellate embryonal connective-tissue cells, while the greater part of the tissue was made up of large spaces filled with a substance which gave the usual reactions for mucus. The fatty parts showed a myxomatous stroma, supporting many fat cells resembling the adult type, as well as numerous embryonal fat cells. In the area of apparent mixture of the two tissues, embryonal fat cells were numerous. The usual myxomatous stroma was found, containing many spaces filled with mucus, as in the purely myxomatous portions. The author relied on the presence of true mucoid material regardless of its origin to place the growth in this group. Regarding the fatty tissue, he considered it reasonable to expect the combination of this with the myxomatous tissue since both are essentially embryonal in character, though of independent mesoblastic origin. He doubts the possibility of myxomatous connective tissue taking on fatty change. The question of malignancy is dealt with cautiously. The frequency of local and metastatic recurrences is to be remembered, as well as the embryonal types of cells making up the growth. In his case, however, the author feels that the definite encapsulation and the quantity of fairly adult fatty tissue are against a recurrence.

The Function of the Bile in Preventing Putrefaction.—Under normal conditions bacteria play an important part in bringing about disintegration of nitrogenous materials of the intestine. Even in health there is a considerable variation in the character and amount of decomposition thus brought about. Metchnikoff and others believed that the products of decomposition developing within the bowel had much to do with organic changes and ill health. For a considerable time it has been claimed that the bile had a direct inhibitory effect upon the growth of the intestinal bacteria and by this means undue putrefaction was held in check. Newer studies have indicated that, save with a few bacteria, bile has little influence upon their growth. Nevertheless, it has been well established that under conditions of bile stasis when little or no bile flows into the intestine, abnormal decomposition of the intestinal contents occurs. ROGER (*Ann. de l'Inst. Pasteur*, 1915, xxix, 545) has recently investigated the problems of determining the influence of bile upon intestinal bacteria and their secretions. He found that bile inhibited the growths of anaërobes but had no marked influence upon the growth of the other intestinal forms. He found, however, that bile had an inhibitory effect upon the fermentative secretions of various bacteria as well as diminished the toxicity of their products. The tests were carried out with various bacteria in the test-tube, while the antitoxic qualities of bile were observed in rabbits. He concludes that the antagonism of bile to putrefaction is not so much dependent upon the inhibition of bacterial growth as upon its neutralizing effect on the secretions of bacteria. It is also possible that bile not only destroys the bacterial ferments but also renders inert their products of decomposition.

ERRATA.—Vol. clii, No. 5, November, 1916, p. 757, after the word "solution" at the end of line 40 the following should be inserted: "of albumose intravenously. The authors were able to confirm these results using a solution."

Ibid., p. 779, line 14: "hemorrhagic" should be omitted; line 15, "vesicules" should be "vesicles."

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DR. GEORGE MORRIS PIERSOL, 1913 Spruce St., Phila., Pa., U. S. A.

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